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Pneumoconiosis

BERYLLIUM

BAUXITE FUMES

COMPENSATION

Leroy U. Gardner Memorial Volume



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PNEUMOCONIOSIS

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Printed in the United States of America

Dedicated to LEROY UPSON GARDNER, M.D.

"... *he devoted his life and talents to the cure of the illness of others and the correction and control of industrial hazards to enable his fellow-men to have better and safer conditions under which to perform their daily tasks.*"

Memorial Minutes, November 17, 1946
Industrial Hygiene Foundation of America

Preface

The literature of pneumoconiosis during the past few years gives evidence of almost unparalleled progress. Close study of the record discloses the advancement of fundamental knowledge of practical significance for the protection of health in industry. Much of that progress could not have been achieved without the combined effort of management and labor, physician and hygienist, chemist and engineer. This collaboration by students of pneumoconiology is indeed a singular tribute to Doctor Gardner who labored so diligently for that objective.

As early as 1934, the late Dr. Leroy U. Gardner, Director of the Saranac Laboratory and of the Edward L. Trudeau Foundation and pioneer in the experimental investigation of the effects of dust on living tissue, instituted the first of the series of Saranac Symposia. He did this in recognition of the need for informal discussion of problems resulting from the inhalation of dusts—problems concerning the industrial, the medical, and the legal phases of pneumoconiosis.

In the following years, at intervals of a year or more, the Second, Third, and Fourth Symposia were held to review the most recent developments in the field of pneumoconiosis and to discuss new problems of current interest. The Fifth Symposium, conducted in 1941, was devoted to Tuberculosis in Industry.

During the war years a new disease which appeared to be caused by the inhalation of dust containing beryllium was recognized in certain industrial employees. The aid of the Saranac Laboratory was sought and Doctor Gardner, with his broad background and knowledge of pneumoconiosis, entered wholeheartedly into the study of the problem. He initiated many clinical and experimental investigations designed to throw light on this puzzling disease. During this period another new disease entity, occurring among workers exposed to the fume arising from bauxite furnaces and known as Shaver's disease, also received his attention.

At the time of his death on October 24, 1946, Doctor Gardner had made plans for a sixth symposium which would consider all aspects of beryllium and bauxite fumes as they relate to industrial health and which would also review the latest developments in the corporate and social responsibilities for pneumoconiosis. It is fitting, therefore, that this record of the papers and discussions by the participants in the Sixth Saranac Symposium, held in Saranac Lake in the fall of 1947, should be dedicated to Doctor Gardner.

The present record of the Sixth Symposium is more detailed than the published accounts of previous sessions. This departure is considered essential because the complex nature of the problems requires a comprehensive and authoritative exposition of present knowledge concerning two most important, but still obscure, pneumoconioses and of the medicolegal problems which they pose Originally, it was planned to publish this material immediately after the end of the sessions. However, unforeseen difficulties caused repeated delays. In the interim, every effort has been made to keep the publication current by developing a bibliography of all pertinent literature concerning beryllium which has appeared up to January 1, 1950.

The enhancement of knowledge which is represented by this record of the symposium is due to those who participated in the formal papers and discussions and whose names are listed not only in the contents, but also in the final pages of the text This record would not be complete without an expression of gratitude to the Lamp Departments of the General Electric Company and of the Westinghouse Electric Corporation, and to the Sylvania Electric Products Inc , The Champion Lamp Works, and the Brush Beryllium Company for their generous contributions which made possible the publication of the proceedings of the Sixth Saranac Symposium.

A. J. Vorwald

Saranac Lake, N. Y.

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PART ONE

The Beryllium Problem

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CHAPTER 1

History of the Beryllium Problem

THOMAS L. SHIPMAN, M.D *

Every physician can understand the excitement of the medical man who encounters what appears to be a new disease entity. Perhaps we have that here, perhaps not. Our story begins in the fall of 1941, when 2 women came under observation at the Essex Sanatorium in Middleton, Mass. Both were complaining of severe and disabling dyspnea, and as their symptoms were primarily pulmonary, it is perfectly understandable that they should have arrived at the local tuberculosis sanatorium. Both had been ill for two or three months, and were obviously extremely ill. Except for the severe shortness of breath physical signs were almost completely absent and the laboratory findings were largely negative. The chest roentgenogram, however, in both cases showed a fine miliary mottling evenly distributed throughout both lungs.

The first diagnostic guess was miliary tuberculosis, but this did not quite fit, and the occupational history would not, it seemed, sustain a diagnosis of pneumoconiosis. Boston consultants, who saw one of the patients in December 1941, made a diagnosis of pulmonary sarcoidosis.

There the matter rested for a time. The 2 women quite obviously had the same condition, but no unusual significance was attached to the fact that they had both worked in the same building of a plant manufacturing, among other things, the then quite new fluorescent lamp. Nevertheless, no one was entirely satisfied with any of the diagnoses so far offered.

By December 1942, the family physician of one of the women came to the somewhat illogical conclusion that his patient had mercury poisoning. Why this particular substance was chosen as the offender I do not

* Works Physician, General Electric Company, River Works, West Lynn, Massachusetts

know, except for the fact that it is used in minute amounts in fluorescent lamps, I suppose it simply seemed a good peg to hang one's hat on. Within a very few weeks that woman died The postmortem observations, which have since become a rather controversial subject, indicated that death was caused by Boeck's sarcoid, and thus confirmed the original clinical and roentgenologic diagnosis. The claim of mercury poisoning was, of course, disallowed.

At this point the subject would have been closed, had not a third patient, a young engineer this time, appeared at the same sanatorium with essentially the same condition. Dr. O. S. Pettingill of the Essex Sanatorium noted the similarity of the findings in the 3 cases. He referred this latest patient to a Boston hospital, and again the diagnosis was pulmonary sarcoidosis The fact that the young engineer had worked in the same building as the 2 women proved disquieting, however. The occupational histories and working conditions of all 3 patients were scrutinized more closely than before, but with entirely inconclusive results.

The director of the Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries at that time was Mr. Manfred Bowditch, who was not one to let such a matter sink into oblivion; on January 13, 1943, a meeting was held at his office to give the subject a complete airing. At this meeting, which I attended, the processes of fluorescent lamp manufacture were discussed by Dr. I. R. Tabershaw,* then physician to the Division The observations at autopsy in the case which ended fatally were described in detail by Dr. Leary. The late Dr. Sampson of the Trudeau Foundation discussed the roentgenologic findings in all cases.

The established facts at that time were these 3 people, 1 of whom had died, were presumed to be victims of Boeck's sarcoid, and strangely enough, all 3 had worked in a building where fluorescent lamps were manufactured Cause and effect, or coincidence? The question remained unanswered In the absence of proof, many of us who were interested were willing to accept the theory of coincidence, although Mr. Bowditch and Dr Tabershaw continued after the meeting to ask some very pointed questions.

Four months later, in May 1943, I was shown a routine chest roent-

* Now with the Liberty Mutual Insurance Company, New York, N. Y.

genogram which strongly resembled those which I had seen at the January conference It turned out that this fourth patient, a young woman, had worked in the same building as the others! A few days later, at the Essex Sanatorium, a fifth case turned up that of a woman who had worked at the same machine as the fourth patient Now excitement mounted. Mr Bowditch arranged another meeting, this time at Rochester in conjunction with the annual meeting of the American Association of Industrial Physicians and Surgeons. Among those present was the late Dr Leroy U. Gardner, then director of the Trudeau Foundation, and from that time on the leading spirit in the investigation

By now there was a tendency to regard the mysterious disease as beryllium poisoning. This substance was suspected probably because among the constituents of the fluorescent powders used in lamp manufacture, beryllium was the only one the toxicology of which was not at least partially understood. Recently, however, Dr L T Fairhall and his associates had published a comprehensive monograph on the toxicity of beryllium, giving the element a pretty clean bill of health [12] * At the Rochester meeting the confusion surrounding the problem was increased by a report on a series of cases of pulmonary disease occurring among workers in beryllium-recovery plants in the Cleveland area [6-26] The histories and symptoms were different from those in the Massachusetts cases, and the roentgenograms were dissimilar Furthermore, although there had been some fatalities in the Ohio series, recovery within weeks was usual

Under the circumstances it was not surprising that this conference reached no earth-shaking conclusions It succeeded, however, in interesting a wider circle of people in the problem There was general agreement that careful and detailed study was required All of us who took part in the investigation were well content to have Dr Gardner act as steersman Wisely the management of the Massachusetts factory provided funds for his research.

At first it was generally expected that the necessary study would require only a few months, but the task proved far from simple The reasons why the study was not successfully concluded within a short time will become apparent in later chapters One incident will illustrate the marches and countermarches which we made in our attack on the problem.

* Superior numbers refer to bibliographic items, pp 599 ff

I thought I had discovered a case in Ohio similar to the Massachusetts cases, this patient too had been employed in the manufacture of fluorescent lamps. Dr Gardner arranged to meet me in the Ohio town in order to explore the situation I arrived in the morning and roused Dr. Cardner at his hotel, and while he was shaving I confidently expounded my theory, I had concluded that we were dealing merely with an atypical silicosis Without missing a stroke in his shaving, Dr. Gardner demolished this theory. He then stated his own: that the fluorescent powders somehow were activated by ultraviolet light, and by radioactivity caused the lesions.

At the end of that day we met an eminent physicist, Dr. Zay Jeffries Having heard Dr Gardner's reasoning, in a moment or two, by devastating logic, Dr Jeffries demolished this theory as completely as Dr. Gardner earlier had destroyed mine Before we met Dr. Jeffries, Dr. Gardner and I had been tired out by tramping through miles of factory aisles, and now as we walked back to our hotel, we were subdued, in fact thoroughly deflated. Suddenly his sense of humor came to the rescue. "Well," he said, with a characteristic chuckle, "I guess we'll both have to think up a new theory tonight"

On October 22, 1943, another conference was held at the Division of Occupational Hygiene in Boston. The gathering included representatives of industry, insurance companies, and state and federal public health services, as well as a distinguished group of medical men and specialists in industrial hygiene Family physicians and others interested in the welfare of the patients also were present, and in some hours of discussion, everyone who had any ideas to contribute had the opportunity to speak his piece The differences between the cases in Massachusetts and those in Ohio were clearly pointed out We were reminded that the 5 cases discovered in Massachusetts were too few to form the basis for diagnostic criteria Some dispute arose about the interpretation of the single autopsy. It was noted that no significant findings had been made in the field of industrial hygiene, and that all the hypotheses offered lacked proof. In short, the problem was not as simple as it had looked

In the following year new cases appeared in Massachusetts, bringing the total up to 14. There were vague reports, difficult to confirm, of possibly similar cases among workers in a New Jersey plant making radio tubes. The acute or "Ohio" form of the disease was reported from

Pennsylvania and elsewhere. Dr Gardner had to spend many hours tracking down shadowy clues

His experimental work produced one extremely interesting result: animals inoculated with beryllium compounds showed malignant changes.[22] Thus some doubt was cast on Dr Fairhall's conclusions. The laboratory animals were uncooperative on the whole, however, for they refused to reproduce the conditions found in man. Material from another autopsy, instead of providing answers to questions, gave rise to new ones

One question which arose in connection with the study concerned the advisability of publishing reports Apparently—no one could be sure of this—the disease observed in Massachusetts was confined to a relatively small group In view of this fact, and because no hearings had yet been held on any claims for compensation, many of those interested thought that it might be improper to publish case reports until the investigation was concluded and a solution could be offered

It was late in November 1944, when the Industrial Accident Board in Boston held hearings on the first 2 cases discovered in that area The defending insurance company held to the theory that the correct diagnosis was Boeck's sarcoid, which is not considered an occupational disease Because definite identification of the disease depended on experimental work which had not yet yielded significant results, the decision was that the claimants should be compensated but that the insurer need make no binding admission of liability It was unfortunate that this hearing was reported inaccurately but extensively in the press, but in one respect the publicity was helpful, for it made it possible to discuss this subject above a whisper

It is easy to imagine the impact of these developments on all manufacturers processing or using beryllium or its compounds. Because this newly discovered metal has tremendous present and potential usefulness in metallurgy, industrialists were hoping that blame for causing the mysterious disease could be fixed on some other substance This still seemed possible. By this time, however, news had come in of cases of the delayed or "Massachusetts" form of the disease among Connecticut workers who had been engaged in processing beryllium-copper alloys,* and if these reports were substantiated, there would be more reason than before to suspect beryllium It was true that though a number of cases

* See Chapter 2 (Ed)

had been connected with one factory in Massachusetts, little or no trouble had occurred in other states among workers in fluorescent lamp factories using similar materials and methods and producing lamps in larger quantities But how was this phenomenon to be explained? What assurance did the other manufacturers have that trouble was not awaiting them in the future?

The publicity dwindled in 1945, but new cases continued to crop up. Though many more animals were "dusted" with fluorescent powders, the experimenters still were unable to produce the disease in the laboratory. Various etiologic theories were evolved, dropped, picked up again. At one time considerable attention was given to some acid-fast organisms in the hope that the disease would prove to be infectious, but this approach led to a dead end

In 1946 we encountered "neighbor" cases, that is, cases of what appeared to be the same disease occurring in persons who had not been employed in the lamp factory but who resided near it And now one fact emerged quite clearly virtually all of the Massachusetts patients had suffered their exposure to the toxic agent, whatever that might be, in 1940 or 1941 The long latent period between exposure and the appearance of symptoms became known as a salient characteristic of the Massachusetts form of the disease

In August 1946, Dr H L. Hardy and Dr Tabershaw published the first real report of the Massachusetts cases[264] using the terms "delayed chemical pneumonitis" and "acute chemical pneumonitis," which have been tentatively accepted and used since that time. Then from behind the veil of secrecy surrounding all the work concerned with atomic energy came the information that beryllium was a matter of interest to workers in this field, though how the metal was used and whether it had caused disease no one could learn We hope that the veil will be lifted a bit higher in this symposium.

October 1946, brought the tragedy of Dr. Gardner's death He had given the investigation such momentum, however, that it could be continued without him. Too much was at stake for the study to be dropped, and fortunately it had become more than a one-man job. In the following year new investigators came into the field

Special praise is due Mr Bowditch for his tenacity in the face of discouraging circumstances and occasional opposition In nearly five years

he never wavered in his determination to see this threat removed from our industry's workers At first competing manufacturers showed some reluctance to join forces even against a common danger, but largely through Mr Bowditch's organizing work they were brought together, their present willingness to cooperate in the investigation is almost unparalleled in industry.

In summary Forty or more persons, of whom 7 or more have died, have been struck down by an unidentified chronic pulmonary disease Another 500 or 600, of whom some have died, have suffered from an acute condition which may be another form of the same disease, or perhaps a distinct entity The chronic and acute conditions have a common denominator, however, in virtually every case we can trace a history of exposure to some compound of beryllium Although the implication is inescapable, proof that beryllium is the toxic agent has been elusive

In this symposium a number of people join in an attempt to put together a gigantic jigsaw puzzle Everyone who could fit a piece of the puzzle into place has been made welcome in the gathering

The beryllium problem presents a twofold challenge to science This element, let me repeat, has rich and varied potentialities for industry, which demands the right to use so valuable a metal If beryllium is dangerous to health and life, we must devise adequate safeguards for those who handle it We are challenged in the field of pure science as well as that of applied science, for we are confronted with a disease, possibly with two diseases, of unknown etiology It is significant that delayed chemical pneumonitis, if it is not Boeck's sarcoid, is closely similar, that it has certain characteristics in common with silicosis, and that it can even resemble tuberculosis enough to make one stop and think Because of the complexity of the problem, let me speak a warning against hasty conclusions Our task demands the humility which insures an open mind

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CHAPTER 2

Beryllium Alloys

ANDREW J. JACKSON, M.D.*

In July 1932, the American Brass Company's branch at Waterbury, Conn., began the casting of beryllium-copper alloys The Waterbury plant is the only branch of the American Brass Company which ever produced such alloys, and is the only Connecticut plant I know of which has processed or used beryllium

Two beryllium-copper alloys were made at Waterbury. One contained 2.10 per cent beryllium and 0 35 per cent nickel, the remainder being copper. The other contained 1 80 per cent beryllium and 0.35 per cent nickel, plus copper. Both were made by melting electrolytic copper and the appropriate amount of nickel with a base alloy consisting of copper with about 4 per cent beryllium.

The melting was done in a crucible furnace known as a Northrup high-frequency furnace in individual heats weighing approximately 500 to 600 pounds The molten metal was then poured under carefully controlled conditions into cast-iron molds which shaped it into slabs for rolling or into billets for extrusion as tubes The slabs were either rolled hot, or cold-rolled, with suitable intermediate anneals into sheet or strip metal of the gage required The billets were extruded while hot as tubes which were then cold-drawn, with suitable intermediate anneals, into tubes of finer gage and smaller diameter, as desired

The boiling points of copper and beryllium are very high, that of copper being 2310° C and that of beryllium being given at 1530° C.† Beryllium and copper are cast at a temperature of about 1150° C. We have

* Consultant, American Brass Company, Waterbury, Connecticut

† Most handbooks of chemistry give the boiling point of beryllium as approximately 1500° C, but this is very close to its melting point of 1350° C. Most metals with melting points near that of beryllium have boiling points near 2400° C. Van Arkel gives the boiling point of beryllium as 2970° C

very little reason, therefore, to suspect the presence of appreciable amounts of metallic beryllium or copper in the fumes which came off the surface of the metal A certain amount of dross always forms on the top of molten metal, and in the case of our beryllium-copper alloys, this dross would have been a mixture of copper oxides and beryllium oxides, with a small amount of nickel oxide.

In the processing of any copper-base alloy, a considerable amount of scrap, such as turnings, sheared ends, and edged trimmings is produced At Waterbury such scrap, whether formed in the rolling mill or the tube mill, was all collected and taken to the scrap room where it was bundled for remelting with new metal in the production of new alloys As in all brass mill operations, there was also a rather large amount of scrap returned by customers for salvaging, and this also was collected and bundled in the scrap room In some cases the scrap was oily, and it was necessary to heat it to a temperature high enough to burn off the lubricant In this burning operation some oxide, or scale, probably was formed on the surface of the metal

The alloys containing beryllium were always melted in one particular furnace, known as the No 1 Northrup furnace, which was located in the southeast corner of the building housing the casting shop, where there was good ventilation through suitable covering hoods and forced drafts to eliminate, as much as possible, fumes which might come off the hot metal This building is a large one, measuring about 178 by 589 feet The casting shop within this building measures 90 by 540 feet in maximum dimension, with an area of 28,260 square feet It is constructed of brick and steel, with three rows of Monitor skylights in the roof, and windows equipped with shutters which can be opened

An exhaust system installed in 1940 draws off as much as possible of the fumes arising from the hot metal There are 42 furnace stations and each furnace has an air-exhaust pipe connected to the ventilation system Suction for this system is provided by four RC-4 Rexvane exhaust fans driven by motors of 5 horsepower, making 600 revolutions per minute Each of these fans is capable of discharging 13,500 cubic feet of air per minute

A ground-floor area of 20,430 square feet, north of the casting shop, on the east side of the building, is ventilated by another RC-4 Rexvane fan, and fans of the same model are installed in the shop north of the

passway on the west side of the building. Beneath this area, in the basement, is the core room The shear room also is located north of the casting shop. This room, which covers an area of 5,568 square feet, has a No. 100 Silent Van fan capable of discharging 20,000 cubic feet of air per minute.

West of the casting shop, and separated from it by a wall of brick and steel, are the scrap room on the ground floor, and in the basement the locker rooms, toilets, and washrooms, and beyond these, a space used for storing metal. Scrap is kept here in bins. This storage section covers an area of 27,540 square feet, and the scrap room above occupies 24,288 square feet

Conveyors approach within about 100 feet of the No 1 Northrup furnace. The scrap room, however, is separated from this furnace by a distance of about 300 feet, and the shear room by a distance of approximately 540 feet

During the past 15 years the number of people employed in this building has averaged 310. The smallest number employed at any one time was 242, in 1932, and the greatest number was 542, in 1943.

So far, 6 cases of sarcoid granulomatosis, or delayed chemical pneumonitis, have appeared among American Brass Company employees. None of these patients was ever engaged in casting alloys containing beryllium One was stationed in the casting shop, doing other work. One worked in the core room, and another in the shear room Two were employed in the scrap department. One worked for a time at the conveyors, and later in the shear room and scrap room.

In 1944, in the period from January 12 to July 14, a series of tests was made to discover how much beryllium was present in the dust in different parts of the building In the southeast corner of the casting shop, where the beryllium-copper alloys were cast, beryllium was found in the following amounts in dust in the top of the flues, 1.03 per cent, in that in the pit, 0 64 per cent, in samples taken at points 2½ feet above the floor, 0 04 per cent, in those taken 5 feet above the floor, 0.02 per cent. On the west side of the building, at points close to the Ajax furnaces and approximately 40 and 80 feet from the No 1 Northrup furnace, dust found 3 feet above the floor contained 0 03 per cent beryllium

In the shear room, 540 feet from the furnace, at 5 feet above the floor, 0 08 per cent was found. In the scrap room, at the magnetic separator, 300 feet from the furnace and 2½ feet above the floor, the percentage was 0 11. In the south passage leading from the scrap room, at a point approxi-

mately 100 feet from the No. 1 Northrup furnace, dust 4 feet above the floor contained 0.53 per cent beryllium.

Another series of tests made in the summer of 1945 gave similar results, the figures being highest for the area where the beryllium-copper alloys were cast, and for the south passage, where beryllium copper was handled and stored.

On October 1, 1946, the American Brass Company discontinued the casting of beryllium alloys, after producing them for 14 years. The casting shop was then thoroughly cleaned by vacuum sweeping. Because further data might prove valuable in future discussions of the effect of beryllium on health, we took advantage of the opportunity which the vacuum cleaning offered to collect more dust samples. This last set of tests indicated clearly that very little beryllium oxide had been scattered through the casting shop, and that exposure to significant concentrations of this substance in dust could have occurred only in the immediate area where beryllium alloys had been cast, or in areas where scrap containing this metal had been handled or stored in some quantity.

In none of the 1946 samples was the beryllium content greater than 0.04 per cent. According to the spectrograph, traces of the element were present in a few samples, although none could be detected chemically; in these instances the amount was assumed to be less than 0.01 per cent.

In all the tests the amount of beryllium was determined chemically, and the presence of the metal was confirmed spectrographically. From the fact that none of the beryllium detected in the dust samples was acid-soluble, we can infer that it was present as the oxide.

Copper values were reported for all but three samples. Other substances found included iron, silica and zinc oxide in large amounts and aluminum in small amounts.

The last series of tests included two designed to show whether beryllium oxide in dross or dust is radioactive. The method used was simple: some dross with a high content of beryllium oxide was placed on a photographic plate and stored for a given period. If any radioactive material were present in the dross, its effect would be to darken the photographic plate, which could be compared with a control plate stored under the same conditions. In the first test, the plate showed no evidence of radiation after six weeks. In the second test, now in process, the plate is to be exposed to the dross for nine months.

Of the 6 cases of delayed chemical pneumonitis, 4 have ended fatally.

A complete autopsy was performed in each instance. Of the 2 patients still living, 1 is failing rapidly. The other is partially disabled, but his condition appears stationary.

The first case which came to our attention was that of a foreman in the scrap department. He was 64 years old, of American antecedents. His period of exposure was 11 years, from July 1932 to August 1943. The onset of his symptoms apparently occurred in 1938. At that time he was being treated for bronchial asthma by a physician not connected with the plant. The patient was not disabled and was able to work with very little lost time, but later he received severe traumatic injuries which resulted in his death on August 3, 1943.

The postmortem observations were.

1. Fractured pelvis with retroperitoneal hemorrhage.
2. Diffuse pulmonary fibrosis with interstitial pneumonitis.
3. Cor pulmonale.
4. Bronchopneumonia
5. Cholelithiasis.
6. Pyelonephritis, chronic

Microscopic study of the lung tissue at the Saranac Laboratory of the Trudeau Foundation revealed sarcoidosis

The second case coming to our attention was that of a young man, 31 years old, American born of Italian parents. He was employed in the core room. His period of exposure was probably about three years. The onset of his illness occurred in 1938. In December 1938 he became disabled and in April 1943, he died. At the time of his death he was assumed to have silicosis, no one entertained the idea that he might have sarcoid disease. At autopsy, however, the observations were as follows:

1. Nodular fibrosis of the lungs
2. Lobar pneumonia, probably tuberculous, of the right lung.
3. Cor pulmonale.
4. Silicosis with infection
5. Lobar pneumonia superimposed upon silicosis.

The lung tissues were sent to the Saranac Laboratory for further study, and the report was sarcoidosis, very closely resembling that in the first case and in the Massachusetts cases.

The third case was that of an Italian, 50 years of age, who was employed in the shear room from July 1932 to November 1944. His period

of exposure thus was a little more than 11 years. His symptoms appeared probably sometime in 1944 In November 1945, this man was sent to the Trudeau Sanatorium for observation and study During his physical examination he had what was assumed to be a coronary attack, and a few days later he died The observations at necropsy were

1 Diffuse pulmonary fibrosis
2 Pulmonary sarcoidosis
3 Dilation and hypertrophy of the right ventricle
4 Splenomegaly
5 Cortical adenomas of the adrenal glands.
6 Benign prostatic hypertrophy
7 Abdominal sarcoid lymph nodes

His lungs were ashed, and spectrographic study of the ash revealed the presence of beryllium

The fourth case was that of an Italian, 52 years old, who was employed in the scrap room as a sorter The period of his exposure was about 10 years, from 1932 to 1942, and his symptoms appeared probably in 1942. In September 1942 he became disabled, and in 1946 he died At the time of his death we believed in Waterbury that he probably had tuberculosilicosis, but when his lungs were sent to the Saranac Laboratory, the case proved to be a positive one of sarcoid granulomatosis The post-mortem observations in this case were

1 Pulmonary fibrosis
2 Cor pulmonale
3 Polycythemia.
4 Right heart failure with peripheral edema
5 Generalized chronic passive congestion
6 Pulmonary sarcoidosis

The fifth case which came to our attention was that of a young man, 24 years old, born in the United States of Italian parents He was employed in the casting shop from 1937 to 1943, and so his period of exposure was approximately six years His symptoms appeared in 1943 In that year his draft board rejected him after a radiograph of his lungs showed fibrosis, which was interpreted by the Army as indicating silicosis He became partially disabled in 1944 He is still living and his condition is more or less stationary At present he is employed as a salesman by a beverage firm He has been examined by the staff of

the Trudeau Foundation on two occasions, and is now suspected of sarcoidosis.

The sixth case is that of a young man, 28 years old, of Lithuanian descent but American born. He was employed as a helper on the conveyors near the casting shop from September 7, 1939, to August 11, 1940, and was a shear operator, cutting nickel and scrap, from August 11, 1940, to December 23, 1944. During the latter period he had a variety of jobs in the scrap room. His period of exposure, then, must be considered as five years. He became disabled in 1944 When he applied for a leave of absence, he stated that he was progressively losing weight, was experiencing shortness of breath, and felt exhausted A radiograph of his chest showed pulmonary fibrosis. This patient has been progressively getting worse. About eight months ago, while he was at the Trudeau Sanatorium, a gland was removed from his left axilla, and this gland gave positive evidence consistent with sarcoidosis

In all these cases the outstanding symptoms were.

1. Marked dyspnea on slight exertion, particularly noticeable on humid days.
2. Paroxysms of coughing The cough was persistent and largely non-productive. No blood was present in the sputum in the first few months of illness, but later on some hemoptysis occurred which was believed to be the result of passive congestion due to cardiac failure
3. Marked progressive loss of weight
4. Intermittent flare-ups of superimposed respiratory infection. During such flare-ups the temperature was markedly elevated and the fever lasted for one to three weeks.
5. Severe exhaustion and malaise

In the periods of acute respiratory infection, penicillin and sulfonamides seemed to have no effect, nor were any results observed from the use of neosalvarsan. Quinine, however, apparently caused a drop in temperature, and seemed to be the only medication that had any effect on the hyperpyrexia. Neither ephedrine nor the morphine derivatives seemed to have any effect in controlling the periodic asthmatic attacks

Physical examination showed all 6 patients to be more or less cyanotic. The physical signs observed by means of percussion and auscultation of the lungs and by means of palpation suggested bronchial asthma. None

of us who were aware of the beryllium problem had an opportunity to examine these men early in their illness and so we do not know whether the physical signs related to the lungs were negative or positive in the early stages of these cases

All these patients were very poorly nourished and showed definite evidence of having lost weight None showed skin lesions.

In all the cases, laboratory tests revealed polycythemia, and during the febrile episodes, marked hyperleukocytosis with a relatively greater increase in the number of polymorphonuclear leukocytes

In all cases the disease of the lungs was characterized by granulomas and the hilar lymph glands were affected At autopsy some of the nodules were found to have undergone degeneration Although the roentgenograms suggested silicosis, the picture differed from that of silicosis in that the nodules were diffused through the whole pulmonary area In no cases were any phalangeal changes revealed by roentgenologic examination

The roentgenologic diagnoses were all studied to eliminate if possible

1 Tuberculosis
2 Syphilis
3 Interstitial pneumonitis
4 Silicosis
5 Asbestosis
6. Chronic passive congestion
7 Primary or secondary tumor other than sarcoid including the lymphomatous type.
8 Sarcoidosis

None of the men engaged in the actual casting of beryllium alloys showed any evidence of pulmonary changes on either clinical or roentgenologic examination Recently the former foreman of the casting shop was examined when he retired after 42 years of employment with the company, and although considerable emphysema was observed, neither clinical nor roentgenologic examination revealed any evidence of pulmonary fibrosis or sarcoidosis

We have noted at the American Brass Company that 6, the number of our cases of delayed chemical pneumonitis, is slightly less than 2 per cent of 310, the average number of people employed simultaneously in the building where beryllium alloys were made From this fact we reason that beryllium oxide is hazardous only for certain susceptible individuals

On behalf of the American Brass Company I wish to express sincere thanks to the staff of the Saranac Laboratory of the Trudeau Foundation for their cooperation and hard work. We are especially grateful for the help given us by the late Dr Leroy Gardner, who took the trouble to

come to Waterbury to study our problem at first hand, and who studied our cases in detail from both the roentgenologic and pathologic points of view. Thanks are due also to Dr. Harold Higgins, who when I consulted him on several occasions was most generous with his time and gave valuable assistance.

Discussion

R. H HARRINGTON, PH D.*

In this symposium the beryllium problem fully emerges, I think, from the confidential stage, I earnestly hope this is true. In the past year or two I have been given certain information and told, "This is confidential. Don't breathe a word" Matters concerning human health and safety should not be kept secret under any circumstances, except at the request of the federal government, which has the right to make such a request.

The metallurgist has much to contribute toward the solution of the beryllium problem, and I urge those responsible for dealing with the all-important medical phases of the problem to seek his direct cooperation. Like the physician, he is a scientist, and will welcome the opportunity to cooperate He is the man who knows the specific conditions under which each specific operation is performed in the preparation or use of a specific material. I warn you, however, that he will insist on justice within his own field. If beryllium oxide, or fluorine associated with beryllium, or zinc beryllium silicate has earned a criminal record, he will not agree to giving the same reputation to an industrial alloy consisting 97 per cent of copper, 2 6 per cent of cobalt, and only 0 4 per cent of beryllium

To avoid confusion I suggest that in relation to their effect on health the various materials containing beryllium be considered in five distinct categories

1 Beryllium oxide.
2. Beryllium compounds other than the oxide
3 Metallic beryllium.
4. Beryllium master alloys
5 Industrial alloys containing beryllium.

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Master alloys are used to introduce beryllium into industrial alloys, this method being preferred for both metallurgic and economic reasons. Examples of master alloys are those containing 3, 5, or 12 per cent beryllium in combination with copper, 5 per cent beryllium and 95 per cent aluminum or 20 per cent beryllium and 80 per cent aluminum; 6 per cent beryllium and 94 per cent nickel, 10 per cent beryllium and 90 per cent iron For special purposes there may be limited use for alloys such as one of 50 per cent beryllium and 50 per cent nickel

Master alloys may be purchased from only two sources, and therefore any possible health problem connected with the production of these materials would be limited to a narrow field It would be far from accurate, however, to restrict the term "beryllium industry" to the two sources of the ingots of master alloys

The industrial alloys are the final mixtures which by recasting or by forging and rolling or machining, with final heat treatment of the solid material, are fashioned into operating parts of finished products. With a few exceptions, these mixtures contain less than 1 per cent beryllium, and usually less than 0 5 per cent The following are examples of industrial alloys

1 1 75 to 2 25 per cent beryllium, with or without 0 5 per cent nickel or cobalt, remainder, copper
2 0 4 per cent beryllium, 2 6 per cent cobalt, 97 per cent copper *
3. 0 2 per cent beryllium, 1 3 per cent cobalt, 98 5 per cent copper.*
4 0 2 per cent beryllium, 1 3 per cent nickel, 98 5 per cent copper.
5 0 1 per cent beryllium, 0 4 per cent chromium, 99 5 per cent copper.*
6 0 2 per cent beryllium, 3.8 per cent copper, 96 per cent aluminum *
7 0 2 per cent beryllium, 3 8 per cent copper, 1 3 per cent cobalt, 94 7 per cent aluminum *
8 0 1 per cent beryllium, 2 per cent copper, 97 9 per cent zinc *
9. Stainless steels containing about 0 7 per cent beryllium

As a metallurgist I am more interested in the alloys than in the so-called pure beryllium metal or in beryllium compounds, and I am especially concerned with the industrial alloys. The published medical reports have not yet given the metallurgist and industrialist any specific information which would help them to determine what precautions should

* Alloys developed and patented by R H Harrington

be taken in producing or using industrial alloys, or even whether any special precautions are necessary.

A quick review of the medical literature on the subject shows that three types of disease are associated with what is loosely called the beryllium industry:

1. A temporary dermal condition, harmful chiefly in forcing the employee to lose time from the job. Cause: irritation of skin abrasions through the handling of metallic beryllium. Precaution: wear gloves. Question: Are the beryllium atoms or ions responsible for this condition, or should we blame the 5 to 10 per cent of fluorine which occurs in the so-called pure metallic beryllium? Another question: Is beryllium metal sometimes slightly radioactive, either because it has been rendered so artificially, or because of impurities in ore from certain sources? Is radiation another possible cause of the dermal condition?
2. Acute pneumonitis, from which a majority of the victims recover. Cause: inhalation. Question: inhalation of what? So far it appears that beryllium oxide, zinc beryllium silicate, and hypothetic beryllium fumes are to blame. Actually any metallic beryllium in fumes would necessarily have become beryllium oxide by the time of inhalation. What other chemicals could be identified in the suspected fumes? In the action of such fumes, what is the role of fluorine? As for the zinc beryllium silicate used in the manufacture of fluorescent lamps, are not the zinc and the silicate in this complex compound open to suspicion at least as much as the beryllium?
3. Delayed pneumonitis, with few recoveries. Cause: inhalation. The same questions arise as in connection with the acute condition.

These are some of the questions to which metallurgists and industrialists want answers. In addition, they want a complete picture of the specific activities in which each affected worker was engaged on the job, and of the specific atmospheric conditions under which the work was done. The mere statement that a certain employee "worked two and one-half months in building X" is irritatingly inadequate.

I should like to discuss briefly certain processes in the production of industrial alloys and in manufacturing with these materials.

Preparation of the Master Alloy for the Melt

An ingot, or pig, of master alloy consists of a row of cubes. For a fairly large melt of industrial alloy, the required number of cubes are broken off the pig with a hammer blow. Most of the master alloys are so tough that hammering produces no fine particles For a small melt, however, less than one cube of the master alloy may be needed, and in such cases a cube must be cut with a saw or an abrasive cutting wheel. Here lie two possible sources of danger

When a saw is used, the waste consists of relatively large chips, but dust may result if these chips are allowed to accumulate on the foundry floor, to be scuffed about for weeks or months When an abrasive wheel is used, the usual guard should be supplemented with a vacuum receiver, or hood, at the lower edge of the guard The General Electric Company has made spectrographic analyses of material collected from the atmosphere surrounding various machines when beryllium alloys were being processed, and these tests indicate that the use of a vacuum hood with the abrasive wheel keeps the beryllium content of the atmospheric dust low enough so that the operator inhales only about 5 micrograms of the metal in an 8 hour day This extremely small amount seems to be well within the limits of safety.

Melting

Even if there were no question of a menace to health, careful metallurgic control still would be necessary in the melting of beryllium alloys, for this relatively costly metal oxidizes readily The usual procedure is one designed to minimize losses. First, the copper, aluminum, or nickel, or whatever metal is to be the base of the alloy, is melted, and then any other ingredients besides beryllium are added The master alloy is put in last When the mixture is such that gravity will not pull the master alloy to the bottom of the crucible, the procedure is to plunge the master alloy below the surface of the melt and keep it there until it disappears in the mixture.

At no time, therefore, is the beryllium content of the melt at the surface higher than the percentage of this metal in the final alloy Because the amount of beryllium reaching the surface is small, the quantity which can escape as vapor is also extremely small Moreover, the relatively scarce beryllium atoms are hindered from reaching the air by surface tension, which causes the formation of a relatively dense layer,

in effect a tough film, at the top of the melt. Another important fact is that many of the industrial alloys are cast at temperatures quite a bit lower than the melting point of beryllium, in such instances the amount of beryllium released in the form of vapor is minute.

When the master alloy is put into the crucible, the top of the melt already is covered with a layer of dross consisting of metal oxides. The beryllium atoms rising into this layer are oxidized by partial reduction of its components, and in the formation of complex oxides are mostly trapped in the dross. Average good metallurgic control restricts the losses of beryllium to the range of 0 01 to 0 05 per cent, and of this amount more than 90 per cent is retained in the dross.

In the case of certain alloys, the probability of illness due to beryllium-oxide vapor released in the melting process may be further reduced by other factors For example, if people were inhaling fumes from melts of an alloy of 0.1 per cent beryllium in a base of zinc, the harmful effects of the zinc would be evident long before the beryllium could do any damage.

Machining

All the industrial alloys of beryllium now being produced possess the property of ductility to a considerable degree, and therefore the chips formed by a lathe or cutter are relatively large and fall immediately by gravity The General Electric Company's tests showed that a lathe operator machining stainless steel containing 0 7 per cent beryllium, for example, inhales only about 0.6 microgram of beryllium in an 8 hour day.

Grinding

Few fine particles are produced in grinding these ductile alloys. Spectrographic analyses of dust suspended in the atmosphere surrounding a grinder showed, for example, that when stainless steel containing 0.7 per cent beryllium is ground, the air breathed by the operator in an 8 hour day contains approximately 0.17 microgram of beryllium, and that the use of a vacuum hood below the guard on the grinder reduces this figure to about 0 02 microgram

Other Operations

Forging, rolling, and heat treating do not produce any chips or dust, nor does good resistance welding. Little, if any, arc welding is done on beryllium alloys, but if this method is used, it should be suspected as a

possible source of trouble. Tests of the surrounding atmosphere should be made and, if it seems necessary, the operator should wear a respirator.

The alloys are so ductile that polishing causes surface flow, and no dust resulting from this process has ever been observed. Nevertheless polishing operations should come under suspicion, and the conditions under which they are done should be investigated

With other members of the General Electric Company's research staff, I have been working with industrial alloys of beryllium since 1930. During the thirties we made tons of such alloys in our laboratory I have been closely in touch with 12 licensed vendors producing industrial alloys under General Electric patents, in some instances since 1936 Our foundry at Pittsfield, Mass, also made beryllium alloys for several years Not one case of any of the three types of disease associated with beryllium has been observed, or I should say recognized, in the laboratory or in any of these plants This does not mean that trouble associated with industrial alloys of beryllium cannot result from poor metallurgic control or the lack of any such control, or from ignorance or downright foolishness It does mean, however, that we can have high hopes of achieving a situation in which no health problems will ever arise in any plant. The price of life and health in any industry is intelligent vigilance based on specific medical information

The foregoing remarks were written before Dr Jackson presented his paper on the experience of the American Brass Company My comments on his report are as follows.

1 Because they are final mixtures used in manufacturing, I have classified the alloys containing about 2 per cent beryllium in a copper base as industrial alloys Their beryllium content, however, is only one-third less than that of the master alloy of 3 per cent beryllium and 97 per cent copper. These alloys with 2 per cent beryllium therefore are border-line cases, and should properly be classified with the master alloys as materials calling for special precautions Even so, the American Brass Company is the only firm to report any damage to health in the production of alloys with this proportion of beryllium.

2 The percentages given before are based on weight, but what actually count are atomic percentages The alloys containing 2 per cent beryllium by weight contain 10 atomic per cent, that is, 10 of each 100 atoms are beryllium atoms The other industrial alloys have only from

2 to about 8 beryllium atoms per 1000 atoms of alloy. Thus the alloys with 2 per cent beryllium by weight contain from 15 to 50 times as many atoms of this metal as do the other industrial alloys. Again we note that Dr. Jackson's company is the only one to have trouble with industrial alloys of the type having the highest beryllium content.

3 Previously I have mentioned the need for careful disposal of the particles produced when ingots of master alloy are cut Dr. Jackson associates some of his company's trouble with a shearing machine and also with the scrap department. One possible source of the trouble is immediately suggested.

4. In this foundry an induction furnace was used to melt the beryllium alloys. An induction furnace causes continuous stirring of the melt by eddy currents By continually breaking the film of dross and thus exposing a fresh liquid surface to the air, this stirring greatly increases the amount of beryllium lost Although in the production of most industrial alloys, for economic reasons such losses must be kept down to about 0.02 to 0 05 per cent of the beryllium in the melt, in the case of alloys with 2 per cent beryllium, losses of 0 1 to 0 2 per cent can be tolerated For this reason the relatively high losses due to induction melting may not have been noticed in the American Brass Company One effect of agitation of the melt, however, is to decrease the proportion of lost beryllium which is trapped in the dross, and to increase the proportion which escapes into the atmosphere Thus induction melting may be one reason why the American Brass Company has had cases of illness, whereas other manufacturers of the same type of alloys have not

Long ago the manufacturers producing industrial alloys under the General Electric Company's patents were specifically warned against induction melting Only quiet crucible melts in furnaces fired with oil, gas, or coke were recommended.

5. With materials other than beryllium, instances have occurred in which fumes issuing from a building were carried back inside by the prevailing winds of the region. This phenomenon is more likely to occur where hoods are lacking over melting furnaces, but it can occur even when fumes are removed by an exhaust system. Perhaps this is what happened at the American Brass Company's foundry. If so, during a period of time the fumes might have collected in the scrap room, even though this room was located at what seemed to be a safe distance from the furnace in which beryllium alloys were made

6 Two cases have been reported of illness associated with a pickling process in which alloys such as those made by the American Brass Company were immersed in an acid bath in order to brighten the surface of the metal. Probably these cases resulted from a lack of adequate vacuum hoods over the tanks In this detailed description of the American Brass Company's building, Dr Jackson makes no mention of a pickling bath, and therefore the sulfates formed in this process can be ruled out as a factor in this company's problem

7. Long before any illness which might be traced to beryllium was recognized, it was known among metallurgists that the American Brass Company's equipment was not ideal for producing the beryllium alloys, and that these alloys did not fit in with the company's other products or its general policy It was known that the company wished to be rid of the chore of making them if it could do so and still supply the demands of its customers Not until the Beryllium Corporation was licensed to produce under the American Brass Company's patents did the latter firm cease manufacturing beryllium alloys (The American Brass Company's patents cover the addition of as much as 0 5 per cent of nickel to the alloys, whereas those of the Beryllium Corporation cover the addition of similar amounts of cobalt.)

The possibility of a menace to health, of course, may have influenced the American Brass Company's decision, but it should not be inferred from this decision that the manufacture of alloys with 2 per cent beryllium is essentially hazardous Such an interpretation would be unfair to other producers, and could be used against them in labor relations. The Beryllium Corporation is equipped to produce these alloys under safe conditions

In conclusion, let me give warning that loose use of the term "beryllium industry" can cause unnecessary confusion in the discussion of engineering problems It can cause loss of time and production through confusion in labor relations Let me also repeat the plea that company physicians work in close cooperation with their companies' metallurgists

Further Discussion

DR PINKSTON Dr Jackson, how many roentgenograms were made of the people employed during that period of years when your company was making these alloys?

DR JACKSON: We had 6 cases—to be precise, 4 cases in which the diagnoses were confirmed at autopsy, 2 patients are still living. Roughly 75 per cent of the employees in the building have been x-rayed. If there was any question of fibrosis of the lung, the films were sent to Saranac for interpretation.

DR SILSON: Dr Jackson, how many histories of general allergic sensitivity were discovered in the cases of those 6 individuals who developed sarcoidosis?

DR JACKSON. In the histories we recorded we could find no evidence of any allergies.

DR CARMODY: I should like to ask Dr. Jackson if in his cases the principal pathologic finding was increased fibrosis, and how extensive it was.

DR JACKSON. That question is going to be fully answered by people working at Saranac *

MR. RICHARDSON: How can you expect that the alloys with 2 per cent beryllium will be cleared of suspicion when we do not know the effect of beryllium on the system?

DR. HARRINGTON. I shall attempt to make my statement clearer. I said I hope that the industrial alloys, except for those with 2 per cent beryllium in copper, will be cleared of any suspicion if the recognized controls are used.

MR RICHARDSON Why do you pick 2 per cent as a dividing line?

DR. HARRINGTON As Dr Jackson has told you, his company has had trouble with 2 per cent beryllium alloys. I tried to suggest some reasons for that Two per cent beryllium in copper is about 10 atomic per cent; one of every 10 atoms is an atom of beryllium I shall never recommend induction furnaces for heating such an alloy.

I am confining my hope—and it's a real hope—to the theory that with proper metallurgic control the alloys containing 0.4 per cent beryllium or less will give no trouble. I have made the statement that as yet no evidence of toxic effects from such alloys has been presented to me, and that in my experience I have known of no case of illness associated with them The alloys containing 0 4 per cent beryllium or less are my particular field of interest.

* See Chapter 11. (Ed)

DR GREENBURG: Did I understand you to say that, in all these years of experimenting in your research laboratory, and in all the years in which General Electric has sold these alloys, you haven't had any cases at all?

DR HARRINGTON: That's absolutely true not one case.

DR BRODKIN: I should like to make some remarks applying to the question raised by Dr. Greenburg and to Dr Harrington's statement. On September 25, 1947, I visited a large New Jersey plant which has been manufacturing fluorescent lamps for several years I inquired of the management whether they had any knowledge of any case of beryllium poisoning developing in their plant. The answer was "absolutely none." I personally know of 3 positive cases of beryllium poisoning which developed in that same factory. Dr Martland reports on 2 fatal cases traced to that factory * When I inquired about one fatal case of the acute disease, they said they were positive that the patient died of virus pneumonia The second case was one of the chronic disease, again the management denied any possibility that the patient could have died of exposure to beryllium The point I wish to make is this industrialists may be innocently unaware of any cases of beryllium poisoning in their plants, but nevertheless such cases may exist, although the beryllium poisoning is not recognized as such The disease apparently is not well enough known by physicians for them to pick cases out

I shall leave further details of these cases to Dr Martland, but I want to present this point at this time because whenever we hear that no case of beryllium poisoning has occurred in a plant in which beryllium is used, the question naturally arises as to whether various cases of illness among the employees have been correctly diagnosed.

DR. MILLIGAN I have two questions. One is in connection with the casting of beryllium alloys is this a sand-casting process, and if so is there any silicosis associated with the sand casting?

DR JACKSON No, there is no silicosis Dr A S Gray of our Connecticut Department of Health personally made the tests in our industry when the question of silicosis arose, and we got a clearance from him. There is no sand used in the casting, of course.

DR MILLIGAN No sand used in casting? The alloys you work with are not cast in sand?

* See Chapter 14 (*Ed*)

DR. HARRINGTON: Yes, the alloys I speak of are poured in sand molds, as well as in metal molds.

DR MILLIGAN I wonder if there might be a dual relationship involving both silica and beryllium or beryllia in this alloy industry.

My second question is whether fluorine or acid radicals have been looked for and considered in connection with the alloy industry?

DR. JACKSON: We never fabricate with any of the beryllium alloys we cast.

DR HARRINGTON· I don't believe that in either your business or ours, Dr. Jackson, there is a possibility of an acid radical coming into the picture, for though beryllium metal produced as such may carry from 0 5 to 10 per cent fluorine on occasion, in the industrial alloys there is no possibility of an acid radical, and the master alloys do not carry fluorine, as the so-called pure metal may.

UNIDENTIFIED SPEAKER Dr. Jackson, did any of your patients show kidney stones at autopsy?

DR JACKSON: None showed kidney stones, one showed nephritis, but no stones.

MR KAWECKI. Since the recent appearance of newspaper accounts of beryllium poisoning at Westinghouse, we have been bombarded with questions from our customers concerning possible toxic effects from the use of beryllium-copper strip and other forms of such alloys We have never heard of any of our customers' getting into trouble; that is, we have heard of no trouble with any of the cold-forming or heat-treating operations. To make sure, we asked one of our customers who uses beryllium copper, I think exclusively, whether he has had any trouble, and we got this letter from him in reply:

"As specialists in making beryllium-copper parts for more than 10 years, we have handled many tons of beryllium-copper wire and strip, and among our more than 100 employees working with beryllium copper daily, we have never experienced any toxic effects No special precautions have been taken other than would be used for handling ordinary copper or bronze"

I should like to ask Dr. Jackson whether any customers of the American Brass Company have ever made complaints or had trouble

DR. JACKSON. Not that I have heard of.

MR. COOK. Have you, Dr. Harrington, had knowledge of any cases of injury to health referable to alloys containing 0.4 per cent beryllium or less, where proper control was not exercised or where the alloys were melted in induction furnaces?

DR. HARRINGTON. We don't know of any cases under any conditions so far.

which have been used in General Electric phosphors. The final powders, after firing, contain less than 1 per cent crystalline silica.

These phosphors are stable compounds under the usual conditions to which they are subjected. They do not deteriorate with use in any lighting fixture. The metallic components of these powders can be hydrolized by strong mineral acids. A fact which may have more direct bearing on our immediate problem is that the phosphors are readily decomposed by 1/1000 N acetic or phosphoric acid. I hope that this symposium will furnish more information on the chemical properties of the phosphors, and especially on the effect of organic acids on zinc beryllium silicate. As some of you may know, zinc beryllium silicate is a loose term for this phosphor. In its preparation there is no atom-for-atom displacement of zinc by beryllium, the final powder is a mixture of zinc beryllium silicate ($[Zn,Be]_2SiO_4$) and beryllium silicate (Be_2SiO_4), as only one-third of the zinc in zinc silicate (Zn_2SiO_4) can be replaced by beryllium from beryllium oxide.

The particle size of the beryllium oxide which we have used was generally less than 3 microns On one occasion during the war a small quantity of more granular beryllium oxide was used In the final phosphors the majority of particles are smaller than 5 microns, by measurement with the electron microscope. The remainder of the particles vary in size, the largest, constituting 1 per cent of the total number, being smaller than 40 microns.

In the early stages of fluorescent lamp manufacture the beryllium content of the phosphors used by different companies varied widely. To the best of our knowledge, General Electric powders had the lowest beryllium-oxide content of all those used in the United States. Because of the necessity of conserving beryllium for the war effort, in Washington, in July 1942, our formulas were offered for the use of all fluorescent lamp manufacturers. It is possible that this date may have importance for the solution of the beryllium problem. I shall be particularly interested if disease of the type we are interested in is discovered in workers who were not exposed to fluorescent powders until after July 1942.

The theory that a low beryllium content in the phosphors is important is somewhat weakened by the fact that 2 of our employees have contracted a peculiar disease in which nodular shadows are seen in roentgenograms of the lungs. Because the course of the illness and the

roentgenologic findings in these cases are closely similar to those in cases reported among employees of other fluorescent lamp manufacturers, all cases probably should be considered as representing similar disease states.

It should be noted, however, that only 2 such cases are known to have occurred among the approximately 8,000 people employed by the General Electric Company in the manufacture of fluorescent lamps during the company's experience in this line Both patients are men Their symptoms appeared in one case two years and in the other three years after the last exposure to phosphors Both had had a somewhat unusual experience for our employees, in that concurrently with their exposure to phosphors, or immediately thereafter, they had been exposed to fumes of hydrochloric and hydrofluoric acid and to toxic substances incident to the manufacture of tungstic oxide and tungsten filaments

This almost minimal incidence of the disease in question deepens the mystery Inquiry has elicited no evidence of unusual illness or loss of working time among our employees making fluorescent lamps

Approximately 100 employees have been directly engaged in the manufacture of phosphors Although early in our experience no unusual precautions were taken to prevent exposure to dust, none of these people has had an illness which can be remotely connected to beryllium exposure. Physical examinations and chest roentgenograms, made yearly since 1943, have been uniformly negative

Many of our employees have now been exposed to fluorescent powders for almost nine years Mass chest x-ray surveys of such employees in the Cleveland area in 1944 and again in 1947 revealed no unknown instances of granulomatous pulmonary disease

As a result of our experiences at the General Electric Company, we have formed the following hypotheses concerning delayed chemical pneumoconiosis.

1 The hazard associated with the ordinary processes of fluorescent lamp manufacture must be small

2 A detailed comparative study of the processes used early by the various fluorescent lamp manufacturers should furnish some clue to the etiology of the disease.

3 Beryllium probably is an etiologic factor in delayed chemical pneu-

moconiosis, but multiple noxious substances must be factors in the causation of this disease.

Further Discussion

DR NICHOL. Has any statistical analysis been made of the incidence of the disease in relation to the number of workers employed in the various processes which Dr Beyer mentions?

MR. MORSE. A simple statistical breakdown of cases in relation to the number of employees engaged in each operation is extremely baffling A number of cases are associated with operations in which few people are employed and in which exposure apparently is slight. Conversely, few or no cases are associated with certain other operations in which many people are employed, apparently with exposure to greater concentrations of beryllium compounds. We do not yet have a measure of exposure accurate enough to warrant drawing any conclusions on this point

DR. HARDY· I should like to add to what Mr Morse has said. A great many at Sylvania Electric Products worked at two or three different stations, so that when you add Mr. Gleason's figures, you get a terrifying number That fact is important in sizing up the situation

DR PINKSTON Dr. Nichol, over how long a period of time were how many of the people followed up among whom no incidence of the disease is reported? You mentioned 8000 employees

DR NICHOL: Again I shall try to be very factual. Four hundred and ninety people were examined roentgenologically in 1944 These people were nearly all those in the Cleveland area who had had any considerable exposure to fluorescent materials They were a truly representative sample

The roentgenograms were reviewed by the tuberculosis group of Cuyahoga County, in which Cleveland is located They were reviewed also at the Saranac Laboratory, whose staff I believe we will agree is competent Without exception, all observers made negative reports for the disease in question

Of some interest is the fact that one person whose exposure ceased in 1942, and whose roentgenograms were negative in 1944, developed all

the manifestations of this disease late in 1945 How do we know that particular *individuals don't have the disease? We do not, from the* evidence we have

In 1947 the examination was voluntary, not all the fluorescent lamp workers were x-rayed We think, however, that again we had a representative sample. I estimate that more than 60 per cent of those exposed were x-rayed These films did not show granulomatous disease of the lungs.

In addition to making these examinations, we have talked to the various managerial groups and to nurses employed in the local dispensaries, and we are basing our opinion partially on their statements I think that such evidence is a little better than it seems I can't conceive of anyone's having the clinical syndrome associated with this disease without manifesting it in such a way as to attract someone's attention Still, I am aware of the fact that cases have occurred in which changes were seen on x-ray examination, though no clinical symptoms were present

DR HAZLETT When we commenced to manufacture fluorescent lamps at Westinghouse, in 1941-1942, we realized that some dust was inevitable, and that, as in any dusty occupation, roentgenologic examination of any person put at that work should be a matter of routine

In 1943 I had the privilege of sitting in on a conference at Rochester,* and of seeing roentgenograms from the cases which were occurring in Massachusetts Of course, at Westinghouse we looked over our roentgenograms and tried to find cases which might perhaps be put in the same classification. But it was not until the spring of 1947 that Westinghouse joined the happy throng. We had been most vigilant since 1943, making periodic x-ray examinations of large groups With this experience, I must agree with most of what Dr Nichol has said in his discussion of the fluorescent lamp industry.

DR SHIPMAN. At the present time I am following up one girl who was formerly employed in a fluorescent lamp factory Her roentgenograms show characteristic changes, but for almost a year she has been symptom-free

DR. NICHOL I think our roentgenograms constituted a fair sampling

* See Chapter 1, page 5 (*Ed*)

The fact is that none of the people examined had a granulomatous disease Different people may interpret this fact in different ways.

There was no important selective factor. Mr. Hughes, did we not examine virtually 98 per cent of the group employed?

MR HUGHES: The 1944 survey covered virtually every person in our fluorescent lamp factory, we made the examination almost obligatory.

DR. NICHOL. There were 490 people included, or 98 per cent of the group in question. None had the disease, although one subsequently manifested it

MR HUGHES. In connection with the question Dr. Pinkston asked a while ago, I believe she might be interested to know that the 8000 people whom Dr Nichol spoke of had roughly 15,500,000 man-hours of exposure That means an average of about 2000 hours of exposure for each individual

DR VORWALD Dr. Nichol, in stating your hypotheses you remarked that beryllium is probably an agent in the causation of this disease we are studying, but you also said something about multiple noxious factors. I wonder whether you would like to expand a bit on that point

DR. NICHOL. I resolved that my remarks were going to be factual, but now they must become highly speculative, for the incidence of the disease as reported by other manufacturers has been high, whereas in my company's experience it has been extremely low. If beryllium or one of its compounds is always involved, there must be a factor common to all cases But that common factor may not be a dominant one, for otherwise I could not explain the marked variation in incidence. I have to assume an additional factor, and I'll say factors, because no single one is apparent.

CHAPTER 4

Present and Future Uses of Beryllium

CHARLES B SAWYER, PH.D.*

In considering the beryllium industry of the present and future from the point of view of health, it is well first to analyze quantitatively this country's past and present importation of ore Our imports are particularly significant for the reason that the United States produces less than 10 per cent of the ore which it consumes, consequently our ore importation is an exceptionally good index of the activity of the beryllium industry Table I gives our annual imports from 1937 through 1946

The only commercial source of the element beryllium at present is beryl, or beryllium aluminum silicate This mineral, found in granitic veins, in its ideal composition contains 14 per cent beryllium oxide, 19 per cent aluminum oxide and 67 per cent silicon oxide In practice we find that the beryl-bearing ore contains about 10 to 12 5 per cent beryllium oxide, the average is perhaps 11 2 per cent, which is equivalent to 225 pounds of beryllium oxide per short ton of ore Imperfect extraction in the plants reduces the amount actually made available to industry to about 170 pounds of beryllium oxide per ton of ore

A short ton of ore yields from 72 to 86 pounds of beryllium metal It is probable, however, that only about 43 pounds per ton, on the average, are extracted in the plants

During World War II something like 90 per cent of the beryllium oxide extracted from the ore was used for producing alloys of beryllium and copper The remainder of the oxide was used principally in the fluorescent lamp industry, although important portions of this 10 per cent remainder went into refractories and light alloys.

It is clear that the requirements of the fluorescent lamp industry are

* Chairman, Brush Beryllium Company, Cleveland, Ohio

small compared to the total amount of beryllium oxide handled in the plants extracting it. In other words, only about one-fifteenth of this country's production of beryllium oxide goes to the fluorescent lamp industry, which is so prominent in the health problem.

Table I gives not only the annual amounts of ore mined in the United States and imported from abroad, but also the amounts of ore stockpiled and the probable yearly consumption The table shows that the beryllium industry began to consume substantial quantities of ore in 1941, and roughly doubled its requirements in each war year for three years. Writing in 1940 for *Metals and Alloys,* I stated that "the ore supply is not unlimited, and were any great demand to appear, the supply might prove temporarily inadequate."

TABLE I NEWLY AVAILABLE BERYL ORE IN UNITED STATES AND PROBABLE YEARLY CONSUMPTION IN 1937–1946

	1937	*1938*	*1939*	*1940*	*1941*	*1942*	*1943*	*1944*	*1945*	*1946*
Short tons										
Imports	182	146	459	805	2666	2050	4840	3115	1201	1181
Production of U. S. mines	75	25	95	121	158	269	356	388	39	50?
Total	257	171	554	926	2824	2319	5196	3503	1240	1231?
End-of-year stockpile	?	?	?	400?	2200	2002	3590	4800	4587	4000?
Probable consumption	?	?	300	600	1200	2300	3100	2100	1200	1400

This point seems to have been reached in 1943, when the United States Metals Reserve Corporation and o[illegible] ernment age though they

Such deposits, however, are unknown at present. The growth of a great beryllium industry like the great tin industry must await the discovery of adequate ore deposits

Beryllium is thought to lie between tin and arsenic in abundance, and to constitute 0 0005 per cent of the earth's crust.

TABLE II ORE REQUIREMENTS OF BERYLLIUM INDUSTRY CALCULATED WITH FORMULA $Y=2X^{2.43}$

Year	*Short Tons*
1931	2
1932	10 8
1933	29
1934	58
1935	100
1936	156
1937	226
1938	312
1939	420
1940	540
1941	680
1942	840
1943	1040
1944	1240
1945	1440
1946	1700
1947	1940
1950	3800

The beryllium industry in the United States really began in the year 1931, when the estimated consumption was about 2 tons of beryl ore. Only rough figures of ore consumption are available for the succeeding 16 years, but the temptation to try to reduce the available data to a formula relating total industrial ore consumption to elapsed years has proved too strong to be withstood The formula arrived at is

$$Y=2X^{2.43}$$

where Y is the year's consumption of beryl ore in short tons, and X is the number of years elapsed since 1930. Table II gives the estimated ore consumption for the years since 1931, as calculated with this formula

The curve resulting from this formula has a smooth parabolic shape, without the irregularities found in the curve of actual experience, the

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This point seems to have been reached in 1943, when the United States Metals Reserve Corporation and other government agencies, though they searched every likely part of the world not under Axis control, could procure only 5100 tons of beryl ore, at approximately four times the prewar price. Apparently, the available supply of ore at present is less than it was then. Thus the slump in industrial ore requirements after 1943 is a fortunate circumstance, if time is required to develop new sources of beryl ore

Perhaps future additional sources of beryllium will be ores of minerals other than beryl, for many minerals containing beryllium are known Perhaps these sources will be lower grade deposits of beryl, made useful by the flotation methods recently developed by the Bureau of Mines

Such deposits, however, are unknown at present. The growth of a great beryllium industry like the great tin industry must await the discovery of adequate ore deposits.

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1933	29
1934	58
1935	100
1936	156
1937	226
1938	312
1939	420
1940	540
1941	680
1942	840
1943	1040
1944	1240
1945	1440
1946	1700
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formula is an attempt to find an average among these irregularities. The figure at a particular point on the formula curve may have to be multiplied or divided by a factor sometimes as great as three to make it conform to a swing of the experience curve. Great as this factor may seem, it is small compared to the total variation in ore consumption during the 16 years beginning with 1931, when about 2 tons were consumed, and ending with 1946, when 1400 tons were used

This formula indicates that subject to a factor of three, the United States beryllium industry's ore requirements in 1950 will be about twice what they are in 1947 In contrast, the demand increased several hundred per cent in each of the industry's early years. This contrast simply means that henceforth the industry's rate of growth will be slower than in the past, and that consequently its employees will be subjected to fewer abrupt increases in the amounts of beryllium to which they are exposed

The properties of metallic beryllium and its compounds are remarkable for the number of extremes which they present. For example, beryllium is about as light as magnesium, but still has a modulus of elasticity greater than that of steel. Although its appearance and chemical stability remind one of aluminum, its melting point is far higher than that of aluminum, it approaches that of iron Thus beryllium has the possibility of usefulness at temperatures at which aluminum and magnesium are softened or melted Beryllium is 17 times as penetrable to x-rays as is aluminum, and therefore is suitable for x-ray-tube windows. Under nuclear bombardment it is the most efficient metallic source of neutrons now known.

The strongest copper-base alloy known is formed with 2 per cent of beryllium, and the same proportion of beryllium makes the strongest known alloy based on nickel Magnesium is made far less inflammable by the addition of an unbelievably small amount of beryllium (0 005 per cent).

Of all known metallic oxides, the oxide of beryllium has the best general properties for making crucibles and electric furnace refractories, though its cost precludes wide use for this purpose Two per cent of beryllium oxide added to zinc silicate broadens the latter's band of fluorescence under ultraviolet light enough to make zinc silicate the most valuable phosphor known

In the field of physiology, also ... [illegible] compounds produce extreme effects.

With so many extreme properties already revealed by this element and its compounds, it seems likely that the discovery of other surprising properties is only a matter of time. Not only will the use of beryllium as at present probably continue to spread, but also new uses probably will be discovered, further increasing the demand for the element. Moreover, as the metallurgic art of using beryllium develops, some of the metal's defects, such as its brittleness, will be diminished, with resultant broadening of its field of application. Its high cost, which is its chief drawback today, also may be reduced as metallurgy advances. In short, I predict that in a considerable period of time the beryllium industry will become as large as its ore supply will allow. As little prospecting for beryllium ore has yet been done, particularly for minerals other than beryl, it is likely that new discoveries will enlarge the base of ore upon which the industry rests.

The use which now accounts for the largest quantities of beryllium is the manufacture of beryllium-copper alloys, of which there are two principal types. The best known type, containing approximately 2 per cent beryllium, can be hardened by heat, and has great versatility. It is like a super phosphor bronze, developing strengths greater than those of stainless steel, and having equal or better resistance to corrosion, especially to corrosion brines. It may be purchased from the mill in the form of sheets or wire, in a wide range of tempers. All these forms are useful for stampings, coil springs, etc., especially when electric conductivity, strength, and endurance are important.

When higher conductivity is desirable, the second type of beryllium-copper alloy, with only about 0.4 per cent beryllium, is employed. It finds particular application in the field of electric resistance welding as the material of the electrodes making contact with the work.

Both types of beryllium-copper alloy are notable for retaining their strength at high temperatures. An alloy of 2 per cent beryllium in nickel also can be hardened by heat, and as a result develops extremely great strength, in some instances as great as 270,000 psi, which is retained at high temperatures. Difficulties in manufacturing this alloy, however, prevent widespread use. Some stainless steels may be hardened by the addition of 1 per cent beryllium, and are capable of retaining their temper at low red heat.

These examples are enough to show that beryllium is an exceptionally potent agent for rendering other metals capable of being hardened by

heat. The effect occurs with most metals, especially when circumstances permit the admixture of a third element in an alloy.

Hardening by precipitation has been noted when beryllium was added to lead or silver, and Dr R H Harrington, research metallurgist with the General Electric Company, has observed this effect with zinc and aluminum The use of beryllium in alloys of zinc or aluminum for die-casting is indicated, and surely some entirely new alloys hardened by precipitation will be found.

An important and increasingly widespread use of beryllium is as an alloying element to ensure the automatic formation of protective films over molten alloys of easily oxidized metals such as magnesium, aluminum, and zinc. The beryllium in the surface layer of a mixture is quickly oxidized to form a tight, strong envelope which protects the bulk of the alloy from further oxidation Such a film is especially effective with magnesium, but unfortunately the addition of beryllium to cast magnesium-base alloys coarsens the grain, and this unsolved problem prevents wider use of beryllium by the magnesium industry.

The protective effect is noted in both molten and solid beryllium copper, and probably occurs with most other metals. It has been observed with silver even at room temperature, when it tends to reduce tarnishing; thus beryllium may prove useful in silverware. Beryllium-oxide film protects certain aluminum alloys when they are handled in the solid state at high temperatures. A possible use for beryllium-oxide protective film is with the electric resistance alloys used for heating elements. To prevent oxidation, beryllium oxide may even be sprayed on tungsten wires and used at high temperatures.

Related to the protective effect of the stable oxide film is the scavenging action of beryllium added to metals such as copper, nickel, and aluminum. This action was observed in Germany during the manufacture of intricate castings for the cylinder heads of air-cooled motors for planes The aluminum alloy cleaned up by beryllium flowed extremely well into the thin sections Thus beryllium has interesting possibilities as a scavenger in aluminum and magnesium alloys to be cast in intricate molds

Probably the only combination of light metals in which a high proportion of beryllium is useful is aluminum with some magnesium In such an alloy for aircraft pistons, for example, beryllium is particularly desirable to give mechanical stability at high temperatures Although the

manufacturing difficulties are great, the addition of 25 per cent beryllium to an alloy such as duralumin produces interesting properties. One of the most remarkable effects is in raising the modulus of elasticity of the alloy from approximately 10, the modulus of aluminum, to something like 17 Moreover, the high thermal conductivity of beryllium is generally maintained to a considerable degree in the alloy. When increased stiffness is required in light alloys, beryllium may be added more often in the future, although this use of the element will still be limited

Improved manufacturing technics make possible the increased use of pure beryllium for the windows of x-ray tubes The metal is highly suitable for this purpose not only because it is easily penetrated by roentgen rays, as I have mentioned, but also because it remains stable at high temperatures An interesting possibility, which comes nearer fulfillment as the mechanical properties of beryllium are improved, is that larger portions of the envelopes of x-ray tubes may be made of this metal, with only enough glass used to insulate the high voltage leads

I have already mentioned the value of pure beryllium as a source of neutrons in projects involving nuclear fission This use will probably increase rather than diminish because of the great relative stability of beryllium at high temperatures under nuclear bombardment

Beryllium's great elasticity and low density permit sound to travel through this metal about twice as fast as through steel This fact should make beryllium valuable in acoustic apparatus—for example, in sound-radiating surfaces, and in general whenever the transmission of vibration without distortion is desired

Beryllium-backed optical mirrors, either oscillating or stationary, are another interesting future possibility

The commercial possibilities of beryllium compounds have received less attention than have those of the metal The best known compound is beryllium oxide Crucibles and electric furnace parts made of it can be used at temperatures 500° C higher than can crucibles and parts made of alumina, and in addition have greater strength and greater resistance to sudden changes of temperature Pure beryllia bonds very well, and at high temperatures retains its high electric resistance The strong affinity of beryllium for oxygen makes beryllium-oxide molds suitable for use at temperatures which strongly favor reduction, and relatively little contamination of melts results from the use of beryllium-oxide

crucibles In the electric lamp industry, the use of beryllia for refractory molds for special purposes may be expected to increase.

Like the metal, beryllium oxide can be used under nuclear bombardment as a source of neutrons, and for this purpose may be employed at much higher temperatures than is the metal.

Zinc silicate modified by the addition of 2 per cent beryllium oxide fluoresces in a broad band under ultraviolet light. It forms the basis of the fluorescent lamp industry, though it is supplemented by varying amounts of one or two other fluorescing compounds, depending on the color of light desired. The combination of zinc silicate and beryllium oxide is highly efficient and therefore in all probability will continue in use.

Beryllium nitrate is used in gas mantles, beryllium stearate in printing inks, and beryllium nitride in the manufacture of carbon 13

Twenty-five years ago beryllium was used only in the form of beryllia, for a single purpose, but today this element has numerous uses of international importance. To one who has watched this development, it is surprising and moving to see how much has been accomplished. Much more work remains to be done, however. The solution of the industry's health problem is vital for progress We may, I believe, feel sure of future success in solving this problem and thus helping the industry to assume greater responsibilities

Discussion

HENRY C. KAWECKI*

I cannot hope to add much to Dr. Sawyer's excellent contribution I shall take this opportunity, however, to say a little about my company's activities and our experience with the health problem. The Beryllium Corporation is fairly large compared with the other two companies engaged in extracting beryllium from ore in the United States. At the present time we have about 400 employees, and during the war had between 600 and 700.

Our experience with pneumonitis has not been bad, though I say that with reservations, perhaps we have not looked hard enough for trouble.

* Research Physicist, The Beryllium Corporation of America, Reading, Pennsylvania

Dr. DeNardi* states that since 1941 the two other companies have had about 400 cases of industrial pneumonitis In 1946 our records listed 10 cases of industrial pneumonitis among our 400 employees. I don't know whether that figure indicates a toxic agent in our plant or not. If we were manufacturing steel, I don't know how many cases we should have had, but they tell me the number would have been smaller than ten

We start with the ore, using a process involving fluorides, not sulfates, to make beryllium oxide We do not make the grade of oxide used in the fluorescent lamp industry, all our oxides go into the manufacture of the metal and of alloys Until it became publicly known that there may be toxic effects from beryllium, we attributed the industrial pneumonitis among our employees to the fluorides which we were using We manufacture compounds and alloys not only of beryllium but also of zirconium and titanium. The work with zirconium and titanium is done in a part of the plant rather remote from the beryllium section and in proportion to the number of people employed in these operations, we have had at least as many cases of pneumonitis and skin trouble as we have had in the beryllium section Therefore it is difficult for us to state conclusively from our own experience that beryllium is the troublemaker

As I have said, we use no sulfates in making beryllium oxide in our plant, but only fluorides In the spring of 1947, however, we had one death, and the man who died was a pickler, his job was to clean beryllium copper which in being heated had been oxidized on the surface This cleaning process consists of placing the alloy in a sulfuric acid solution, the resulting solution being one of copper sulfate and beryllium sulfate The pickling tank is the only place where beryllium sulfate is present in the plant, and beryllium sulfate may be a troublemaker

I should like to call attention to the fact that the other two extraction plants produce beryllium oxides for the fluorescent lamp industry, and, I understand, use processes different from ours Perhaps someone should undertake to correlate the health problem in the various fluorescent lamp plants with the processes employed at the sources of the beryllium oxide

The Beryllium Corporation, of course, is very much worried about this problem We hope that our record in the future will be at least as good as it has been in years past We have got the Division of Industrial Hygiene of Pennsylvania's Department of Labor interested in the prob-

* See Chapter 7 (*Ed*)

lem, and recently they made an x-ray examination of everyone in the plant.

I should like to add to Dr. Nichol's remark that people may work a long time with beryllium without being affected * I have been breathing beryllium fumes of every type for more than 13 years, and yet here I am We have had people working for a long time in the most dusty atmosphere in the plant, in the spot where beryllium oxide is heated to a high temperature and then shoveled out of the furnaces. The shoveling is a dusty occupation. Yet one man has been engaged in it for 13 years, another for 15, and another for 17 years. Certainly, therefore, not everyone is susceptible to the possible toxic effects of beryllium.

Further Discussion

DR. VORWALD. Mr. Kawecki, have you had an x-ray examination of your chest?

MR KAWECKI. I had one in August 1947. I also had an x-ray examination two years before that, and each year previously for three or four years, at my own expense

DR. SCORNAVACCHI As plant physician, I have had several of the 10 pneumonitis patients whom Mr Kawecki mentioned under my care. The case of the man who died is going to throw another monkeywrench into the machinery and even make the problem a little more interesting, for the diagnosis given by the pathologists—six or seven of them—was like that in the cases at Saranac, and the microscopic picture was exactly the same

The other 9 patients have been followed up and re-examined roentgenologically Eight are free from symptoms now. The ninth is a man whose illness I discovered within the past week, and who now has a fulminating respiratory infection, if you want to call it that Laboratory data are negative, and so the future must solve this problem

Most of our trouble at the Beryllium Corporation has occurred in the pickling department which Mr Kawecki mentioned, where the employees are in contact with sulfuric and nitric acid fumes. Three of our cases, including the one which ended fatally, originated in that department. In the short time I have been with the company my theory has been—I am just mentioning a theory—that the sulfuric acid radical or the fumes,

* See Chapter 3, page 35 (*Ed*)

in contact with the moisture of the lungs, produces sulfuric acid pneumonitis.

Though we handle as much beryllium or more than do many other plants, our problems have been less serious than theirs, I should say. Ten cases during a period of so many years is a fairly good record, though the one death is a serious matter

DR AUB In this particular job, was the beryllium alloy of one particular kind?

MR KAWECKI. Most of it was 2 per cent beryllium in copper.

DR AUB. You were simply trying to remove the oxide from it?

MR KAWECKI The metal was already cold, but bubbles were rising in the solution.

DR VORWALD I should like to clarify one point. If I am correct, Mr. Kawecki, you incriminated the fluorides used in one process in your industry, but did not incriminate those used in other processes

MR KAWECKI That is not what I meant We have a certain amount of trouble in our zirconium and titanium department, as well as in the beryllium department.

DR VORWALD And you have not seen cases of pneumonitis in the other department?

MR KAWECKI. Yes, we have—at least as many as in the beryllium department

CHAPTER 5

A Common Denominator

CHARLES R. WILLIAMS, PH D.*

A common denominator is "a combination of terms, subject matter, or the like equally agreeable to all of a group" (Webster). This is precisely what we are trying to find for the various phases—medical, experimental, chemical, and engineering—of the investigation of the beryllium problem We are trying to gather data which are consistent with each other and to fit them into a pattern which logically explains what happens to people when they inhale certain beryllium compounds. In addition, we are seeking a means of protecting people from exposures which injure health

We are dealing with at least two phases of a disease peculiar to industries using beryllium in many forms. In many respects the two phases present two distinct problems. The acute form of the disease appears to be the result either of heavy doses of beryllium oxide or of varying degrees of exposure to beryllium fluoride, beryllium chloride, beryllium sulfate, and similar compounds This phase seems more clearly definable than the other, although there are confusing elements such as manifestations which apparently are allergic, and occasional cases in which the exposure was slight In most cases, however, inhalation of a beryllium compound definitely occurred, and in general this form of the disease most frequently is associated with the plant areas where the heaviest concentrations of dust occur.

The fundamental controversy concerning the acute form of the disease centers on the relative significance of beryllium and the acid radicals of certain salts. This controversy is illustrated by the entirely different approaches to the problem taken by the authors of two papers describing

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hazards to health in the basic beryllium industry. In 1944 Shilen[518] and his associates made an industrial hygiene study of a beryllium-producing plant in Pennsylvania They dismissed beryllium as a pathogenic agent, and reported atmospheric concentrations of fluorides and oxides of nitrogen to which they attributed the respiratory disease and dermatitis occurring in that plant In 1945 VanOrdstrand[526] and his associates, however, in a paper titled Beryllium Poisoning, described 170 cases of pneumonitis among the employees of a plant performing operations similar to those carried on in the plant described by Shilen VanOrdstrand and his associates consider beryllium an important causative factor in these cases

This fundamental difference of opinion must be resolved for proper understanding of the acute pneumonitis The question, of whether beryllium, the acid radicals, or a combination is the cause, must be answered.

In the so-called delayed pneumonitis there are many factors which are foreign to the usual pattern of occupational disease The low incidence, the lack of any established relation to the degree of exposure, and the long delay in the onset of symptoms in many cases all make for confusion Ordinary methods of attacking an industrial hygiene problem were of little value early in the investigation It was disconcerting to find severe illness developing in workers who had suffered only slight exposure, whereas hundreds of employees doing what were visibly more dusty jobs remained unaffected The incidence was low in one plant, and in others making the same product, no cases were found Then cases developed four and five years after the cessation of exposure

When the first cases of respiratory disease appeared in the fluorescent lamp industry in 1941, their cause was not apparent In fact, they were so few in relation to the number of employees that there was a reasonable doubt of their occupational origin As the number of cases increased, however, attempts were made to find a common denominator in the industrial environments Several environmental factors were noted which might possibly contribute to causing disease, but only one of these factors was obviously common to all the cases This factor was employment in a particular building where fluorescent lamps were manufactured. Although beryllium-containing phosphors obviously were what most of the patients had inhaled, one or two patients had not been directly exposed to the phosphors Subsequent investigation, however, including

inspection by means of ultraviolet light, revealed that the entire building was under negative pressure and was contaminated. Still, several of the patients had been exposed only very slightly.

Late in 1941 the operations performed in this plant were transferred to a new building with excellent ventilation, and it was generally believed that the disease would disappear. The first few cases of illness reported in the new building were all among employees who had been exposed in the old building, and so the original theory still seemed valid. Eventually, however, the disease appeared in an employee who had worked only in the new building. This case was followed by others like it, and a new common denominator was sought.

By late 1946, 36 cases had appeared, and all the patients possibly had been exposed to a particular group of phosphors containing either about 6 or about 12 per cent beryllium oxide in the final mix.

Sometime in 1943 the amount of beryllia in the phosphors was decreased to approximately 2.5 per cent. It may be significant that no employee in this plant has yet contracted the disease who was hired since the use of the phosphors with the higher beryllium content was discontinued. Moreover, no undisputed cases of the disease have appeared among the employees of manufacturers using phosphors with 1.5 or 2.5 per cent beryllium oxide in the final mix. It is entirely possible, of course, that the disease merely takes longer to develop when the exposure is to phosphors with a low beryllium content. Or we may be dealing with different compounds of widely different toxicity.

Quantitative atmospheric analyses were not possible in the early stages of the investigation because a reliable method for determining the amount of beryllium in the air was lacking. The atmospheric concentrations which produced these 36 cases therefore will never be known.

In addition to the cases in the fluorescent lamp industry, cases of delayed pneumonitis appeared also in other industries using beryllium compounds, and so beryllium became suspect. Now the entire problem is being attacked in a systematic way. The investigation is going to be a tedious one for the usual routine methods for attacking industrial hygiene problems will not yield quick or spectacular results.

The magnitude of the beryllium problem obviously is determined by the uses to which this metal and its compounds are put. Lamb[354] states that "possibly the main factor preventing the use of more beryllium is

the lack of a large source of beryllium ore." The production of beryl, the only important ore of beryllium, has never exceeded a few thousand tons annually.

As beryl contains only about 5 per cent beryllium, it is evident that on a tonnage basis the metal with which we are dealing is a relatively unimportant one Nevertheless, because in many of its uses only minute quantities of beryllium are required, the possible danger to industrial workers is considerably more widespread than might be expected from the production figures

At the present time the more important industrial operations involving beryllium and its compounds are as follows:

Mining and Milling of Beryl Ore

Mining and milling operations involve the handling of the beryllium aluminum silicate (beryl) In the United States these operations are performed on a small scale, and the industry is scattered over many states No data are available on the possible effect of inhalation of this compound

In the past, much of the ore has been processed by hand, the beryl crystals being picked out of the matrix material Recently, however, intensive studies have resulted in the development of flotation methods for separating beryl from associated minerals These methods will make possible the utilization of many ore deposits which formerly had no commercial value

Extraction of Beryllium

Far more important in relation to occupational disease are the metallurgic processes necessary to extract beryllium from its ore In the extraction plants, employees are exposed not only to beryl but also to beryllium oxide, beryllium sulfate, beryllium oxyfluoride, basic beryllium carbonate, beryllium chloride, and beryllium metal Many cases of dermatitis and acute pneumonitis have been reported from this industry, but the roles of the various compounds have not been determined

Manufacture of Ceramics

For many years beryl has been used in the ceramic industry to clarify chrome colors in vitreous enamels and to provide desirable qualities in electrical porcelain. Beryl substantially increases the strength of porcelain, its dielectric rigidity, and its resistance to changes in temperature,

and decreases shrinkage in firing. As much as 40 per cent beryl may be used in this material. No cases of occupational disease resulting from such use of beryl have been reported.

During recent years beryllium oxide has acquired increasing importance as a ceramic material because of its refractory quality. Fused beryllia is a particularly suitable material for ceramics to be used at temperatures near 4000° F. It is used for crucibles for casting metals with high melting points, for linings for high temperature furnaces, for electrical insulators, combustion tubes, and so forth. The manufacture of these refractory products involves the handling, screening, and milling of beryllium oxide All these operations can be extremely dusty, and have given rise to cases of acute pneumonitis.

Manufacture of Alloys

By far the most important use of beryllium in alloys is with copper, the result being an unusually hard, corrosion-resistant, nonsparking alloy with particularly desirable electrical properties and high conductivity for heat. In addition, beryllium is becoming an increasingly important alloying material for steel, aluminum, nickel, and magnesium. Exposure can occur during the melting of these alloys as well as during subsequent machining and grinding. Several cases of delayed pneumonitis have appeared among the employees of one foundry making beryllium-copper alloys.

Manufacture of Fluorescent Lamps

The most important phosphors used in the interior coating of fluorescent lamps contain small amounts of beryllium oxide The workers engaged in making the phosphors are exposed to beryllium oxide and zinc beryllium silicate as well as to silica, zinc oxide, cadmium oxide, magnesium oxide, tungsten trioxide, and boron trioxide. Those engaged in applying the coating to the lamp tubing are exposed only to zinc beryllium silicate.

In this industry acute pneumonitis has appeared among workers making phosphors and delayed pneumonitis among those manufacturing lamps The former occupation was found to be accompanied by heavy concentrations of dust in the air, whereas in lamp manufacture, the exposure was generally of a low order, although heavy concentrations of dust, of brief duration, occasionally resulted from broken bulbs or special operations

Exposure may occur in plants manufacturing so-called neon signs, for the phosphor used is identical to that used in fluorescent lamps. Powders containing beryllium oxide are used also in the manufacture of electronic tubes and similar articles.

Miscellaneous Manufacturing

Many minor uses of beryllium compounds might be noted. For example, small amounts of beryllium nitrate, usually less than 0.5 per cent, generally are used in solution to strengthen the ash skeletons of gas mantles. Beryllium metal is used in the windows of x-ray tubes because of its transparency to roentgen rays and its resistance to heat. The use of beryllium alginate in the production of synthetic fibers has been reported from England.

The aforementioned uses of beryllium and its compounds, together with their use in studies of atomic energy, account for most instances of exposure at the present time. Apparently beryllium in some form is always a factor in causing both forms of the peculiar type of pneumonitis with which we are concerned. Yet pneumonitis does not appear everywhere beryllium compounds are used. It does not invariably accompany exposure to specific compounds. Among fluorescent lamp factories its incidence has varied widely, it has appeared in one foundry making beryllium alloys, but has not been found throughout that industry, occasionally someone engaged in bending fluorescent tubing for neon signs has been affected, but hundreds of sign-tubing plants have reported no cases.

We are faced with the fact that beryllium in some form is the common denominator in these cases of pneumonitis. Pneumonitis, however, is not common to all cases of exposure to beryllium, beryllium alone does not explain all the facts. Considerably more data are needed, and the following questions must be answered.

1. What is the relation between the acute and chronic forms of the disease?
2. In the chronic form, what is the cause of the delay in the onset of symptoms?
3. What is the significance of the low incidence of the chronic disease?
4. Can beryllium alone cause pneumonitis, or are there other factors as yet unknown?

6. Are ingestion of beryllium or absorption through the skin causative factors?
7. What is the fate of beryllium in the body?
8. Which beryllium compounds are toxic and which are not?
9. What levels of atmospheric contamination cause either acute or chronic pneumonitis?
10. Are there different levels of safety with different beryllium compounds?

When these and many other questions have been answered, and only then, will the role of beryllium in this industrial health problem be clearly defined.

Discussion

EDWARD C. J. URBAN, M.S *

Instead of discussing the specific subject matter of Dr. Williams' excellent paper, I shall supplement it with some observations made recently in the Saranac Laboratory's engineering studies undertaken for the purpose of correlating the results of the Laboratory's research with industrial experience. So far we have visited 20 industrial plants, in which a total of 3500 workers are employed, in order to study the ways in which beryllium and beryllium compounds currently are produced and used, and the various occupations in which exposure to beryllium might occur. Similar surveys in other plants are planned for the near future.

Beginning in late 1946, we approached more than 50 different producers and users of beryllium and its compounds for permission to make such surveys, and received most gratifying response In all the plants which we visited, the managers and supervisory personnel were cooperative and showed no lack of interest in any aspects of the health problem which might affect their employees Their attitude does credit to them as individuals and to their industry as a whole, especially in view of the fact that some of these men had had no previous contact with the Saranac Laboratory, and that in a number of the plants, to the best of the management's knowledge no occupational disease had appeared which could be connected directly with beryllium.

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The different ways in which we found the element and its compounds being used are illustrated schematically in fig. 1. As this chart is based on data from 20 plants with a considerable number of employees, some of the generalizations which may be developed from it can properly be applied to the beryllium industry as a whole

Beryl is a mineral of igneous origin, occurring in pegmatite, and is a by-product of feldspar mining A good grade of ore contains about 12 per cent beryllium oxide, which is equivalent to about 4 per cent metallic beryllium Almost all the beryl used in the several beryllium-extraction plants which we visited was obtained from South American sources

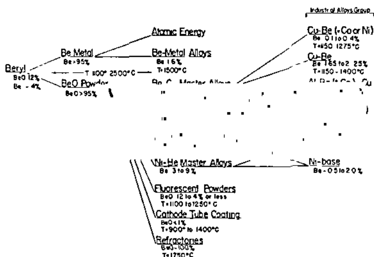


Fig 1 Uses of beryllium and beryllium compounds in 20 industrial plants, classified by the beryllium content of the products and by the temperatures at which the materials are processed

These plants produce beryllium metal, highly purified beryllium oxide, and the so-called master alloys of various amounts of beryllium in solid solution with other metals such as copper, aluminum, iron, and nickel. In the preparation of these products sulfuric acid and fluorides are used, and the materials are heated frequently in ovens or electric furnaces, at temperatures ranging from 1100° C. to 2500° C. and higher Factors in the occupational environments are the various stages of the extracting process, various combinations of beryllium with other toxic agents, and the effectiveness of the safeguards provided in connection with processes

in which chemical reactions are accelerated by heat or by other operations performed nearby. It has been mostly in these extraction plants that the acute form of pneumonitis has occurred.

Beryllium metal, we learned, was being used in atomic energy projects, but we have no further information on this use of the element.

In one of the plants surveyed, highly purified beryllium metal is added to a molten mixture of chromium, cobalt, nickel, and molybdenum to form an alloy containing 1.6 per cent beryllium. The combining is done at a temperature of about 1500° C. This alloy, developed in 1931, since then has been used in the manufacture of dentures and dental restorations. We were informed that more than 300 licensed dental laboratories in this country are using this alloy. Examinations of the workers engaged in making the alloy and of a number of technicians who fabricated the dentures failed to reveal definite evidence of disease which could be associated with their occupations.

A common use for beryllium-oxide powder is in the production of master alloys of beryllium copper. These master alloys, which serve as carriers of known amounts of beryllium, may contain from 3 to 12.5 per cent of the element, but the type most generally used contains 4 per cent. Weighed amounts of beryllia, pure copper, carbon, and dross from previous melts are combined. The mixture is brought to a high temperature, ranging from 2000° to 2500° C. or more, and then cast into small pigs or ingots.

The master alloy prepared in an extraction plant is used sometimes in the same plant, but more often in other plants, in the production of the industrial forms of beryllium copper. In the foundries we visited, industrial alloys containing from 1.65 to 2.25 per cent beryllium were made by combining specific amounts of master alloy with industrial beryllium-copper scrap, pure copper, and carbon in electric furnaces at temperatures ranging from 1150° to 1400° C. The resulting products were cast into ingots and then cold-rolled into strips, sheets, wire, rods, bars, and blanks suitable for fabrication.

We found master alloys containing beryllium in the concentrations noted in fig. 1 being used in plants other than the extraction plants, in the manufacture of specific industrial alloys. For example, a master alloy of beryllium copper can be combined with a ternary master alloy contain-

ing zinc in the manufacture of a zinc-beryllium-copper industrial alloy to which aluminum also may be added Likewise, beryllium-copper and aluminum-beryllium master alloys can be combined in an aluminum-beryllium-copper industrial alloy to which cobalt may be added Some of the more common combinations, with the beryllium content in each instance and the temperature at which alloying is done, are indicated in fig 1.

Two important distinctions between master and industrial alloys should be noted the proportions of beryllium in the latter are much less, and the alloying is done at lower temperatures It is noteworthy also that after the industrial alloys have been melted and cast, many of the subsequent operations, such as cold-rolling, shearing, pressing, and stamping produce relatively little dust and fumes

Probably the most widely known use of beryllium oxide is in the powdered phosphors used in fluorescent lamps. Although some fluorescent powders have been made with as much as 12 per cent beryllium oxide, the phosphors now most commonly used contain 4 per cent or less The beryllia is combined with the other components of a powder, and the mixture then is sintered at temperatures varying from 1100° to 1250° C. to obtain the necessary zinc-beryllium-silicate combinations and the desired crystal structure. Many of the known cases of the chronic type of pneumonitis have originated in the fluorescent lamp industry

One of the less important uses of beryllium oxide is in powders for coating cathode tubes Such cathode tubes are used in television apparatus, the coatings being the viewing screens upon which the televised images appear Not all the coatings contain beryllium oxide, and when it is used it is present in concentrations of 1 per cent or less. The other components of the powders are somewhat similar to those used in phosphors for fluorescent lamps When the beryllia has been added, the desired combination of elements in crystals of the proper size is effected by firing at temperatures ranging from 900° to 1400° C.

Beryllium oxide is used also in the manufacture of refractories. In the plant which we visited, small laboratory-type crucibles are made almost entirely of beryllium oxide The beryllia first is sintered at 1750° C. into a hard compact mass, and then reduced to grains of the proper size by crushing and screening When the crucibles have been shaped into the

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desired form, they are fired at a somewhat lower temperature, for hardening.

Three important conclusions can be drawn from the data which we have gathered.

1 In the production of beryllium and its utilization in industry the element sometimes is present in virtually pure metallic form, but in most processes is present in various combinations or compounds, in widely varying degrees of concentration The concentration is determined by the particular stage of the extraction process or by the specific purpose for which an alloy or compound is intended. We found that more than 70 per cent of the employees in the plants we visited handled some compound or alloy containing only 4 per cent beryllium or less

In most of the industrial end products the beryllium is present not in simple physical combination with other elements, but in an intimate mixture or solid solution closely approaching chemical combination.

2. Many processes in the production and utilization of beryllium include heat treatment, but at widely varying temperatures Figure 1 shows a range of temperatures from 450° to 2500° C.

3 During the initial period after the introduction of beryllium into industry, compounds were employed in which the beryllium content was higher than in those used for the same purposes today. We learned from a manufacturer of an industrial type of beryllium copper, for example, that from 1931 to 1937 his plant used a master alloy containing 12 5 per cent beryllium, but that in 1937 the proportion was reduced to 4 per cent Similarly, some manufacturers of fluorescent lamps reported that from about 1939 to 1941 they used phosphors containing as much as 12 per cent beryllium oxide, whereas today the usual proportion is 4 per cent or less.

It is obvious that the factors which must be considered in any problem of disease associated with beryllium include (1) the proportion of beryllium in the material handled, (2) the state in which the beryllium is associated with other elements, that is, whether in physical or chemical combination, (3) the possible association of beryllium with other toxic agents, and (4) the temperature at which the specific process is performed. It is apparent also that . ›ledge of the nature and history

of a particular job is essential for evaluation of the possible hazard in that particular working environment.

Further Discussion

DR AUB In conversation Dr Williams has mentioned a case of chronic pneumonitis in which the patient lived 400 feet from a fluorescent lamp factory. I am taking this opportunity to ask him how this woman got the disease

DR WILLIAMS The fluorescent powder to which the woman was exposed had three possible sources. It was possible though it seems unlikely, that the disease was caused by the powder which another member of the household, a girl employed in the lamp factory, may have brought home in her clothing The lamp factory itself was another possible but unlikely source The most probable source was a second nearby factory, one in which phosphors were made. The patient said that she had to sweep white powder off her back porch The manufacture of phosphors is a fairly dusty operation, in this instance undoubtedly some powder escaped from the plant into the outside air, and it happened that prevailing winds blew in the direction of this poor lady's house. After her death, spectrographic examination showed beryllium in her lungs

Dozens of other people lived in the same neighborhood, and this fact brings us right back to where we started

MR HUGHES I want to say that the General Electric Company has prepared instructions to give to all customers in regard to the breaking up and disposal of fluorescent lamps out of doors

DR SAWYER. One of the points in Dr Williams' paper which interested me was the fact that he considers the volume of beryllium handled in a given plant not only by itself, but also in relation to the number of employees in that plant

In my paper I stated that about one-fifteenth of the beryllium oxide produced by the extraction plants goes into fluorescent lamps Yet, from figures I have heard I gather that the number of employees in the fluorescent lamp industry is much greater than the number in the plants producing all the oxide What does this mean To me it indicates that beryllium oxide must have a rather pronounced effect in the form in

which it is compounded for use in lamps, for though the amount per worker is small, quite a number of cases of disease have originated in this industry

Mr. Kawecki, your company, I understand, operates a rolling mill My company has no rolling mill, but nevertheless the volume of beryllium oxide handled in each of the two plants probably is about the same. When that fact is taken into consideration I think you will find that the exposure is about the same in the two plants. Do I make that point clear, that the volume of a product such as beryllium oxide is important as well as the number of employees?

PART TWO

The Beryllium Problem

The Acute Disease

CHAPTER 6

Acute Beryllium Poisoning

H S VANORDSTRAND, M.D *

My purpose is to describe the over-all picture of the pathologic conditions encountered in northern Ohio in workers engaged in the recovery of beryllium from the ore beryl This paper is in the nature of a summary of observations made by a group of five, I am speaking not only for myself but also for Dr Carmody of Painesville, Ohio, Doctors DeNardi and Zielinski of Lorain, Ohio, and Dr Robert Hughes, who is head of the x-ray department of the Cleveland Clinic Our experience with the problem dates from 1940, when the first death occurred.

From the beginning we were struck by several facts

1 The pneumonitis cases showed diffuse, symmetrical, bilateral lung involvement, which is a common characteristic of occupational pulmonary disease

2 The pathologic conditions under discussion here occurred only in workers engaged in extracting beryllium specifically

3 The trouble recurred when patients returned to the same employment

4 The clinical and roentgenologic observations in these cases were strikingly similar to those in the cases resulting from our tragic disaster at the Cleveland Clinic in 1929

5 Marked variation in individual susceptibility was obvious

6 The pathologic conditions observed in human beings were not reproduced in guinea pigs exposed at the same locations in the plants

The first patient whom we had an opportunity to study at the Cleveland Clinic Hospital had been a co-worker of the patient whose death brought

* Physician, Cleveland Clinic, Cleveland, Ohio

the problem to our attention. The clinical picture was that of moderate pneumonitis. In this second case we were able to make a rather extensive study, including a bronchoscopic examination, and the complete picture indicated an irritant of chemical origin, the absence of anything at all suggestive of primary inflammatory disease was striking.

The roentgenograms were sent to the Saranac Laboratory to Doctors Leroy Gardner and Homer Sampson, whose interest was aroused We were fortunate in having their help at this early stage. In this case the Industrial Commission of the state of Ohio acknowledged the existence of an occupational disease. I want to express appreciation of the complete cooperation of the Commission and of the employers, who from the *beginning recognized the nature of the problem and made persistent* efforts to solve it.

As Dr. DeNardi mentions,* among the beryllium workers at Lorain he and Doctor Zielinski have recorded more than 300 cases, each of one or more of the disorders which we have observed. The Painesville plant, though smaller, has had a comparable amount of trouble in relation to the total number of employees, for certainly more than 100 cases have occurred It seems safe to say, therefore, that in the two plants more than 400 workers have been affected The most serious problem has been acute pneumonitis, of which we have had nearly 100 cases, with 6 fatalities

The clinical manifestations in all these cases are of two types: (1) dermal and (2) respiratory. The areas affected are shown in fig 2.

The dermal manifestations consist of (1) contact dermatitis, (2) conjunctivitis, (3) corneal burns, and (4) the so-called beryllium ulcers.

The contact dermatitis appears on the exposed surfaces of the body, particularly on the face, neck, arms, and hands, and consists of a maculopapular eruption Often it has appeared in susceptible individuals by the end of the first week of employment. Dermatologists who have seen a number of these patients agree that it is hard to differentiate this eruption from ordinary types of contact dermatitis. An example with facial involvement is shown in Plate I (A). The affected workers, if allowed to continue in employment, usually have developed other, more serious disorders As Doctor DeNardi mentions,* the contact dermatitis has proved

* See Chapter 7 (*Ed*)



A



B

PLATE I

A Contact dermatitis of the face in a worker exposed to beryllium fluoride
B The 'beryllium ulcer' which commonly occurs on or near a knuckle, at the
ite of an antecedent abrasion It is indolent and persists until its base has been
xcised

to be a definite sign of individual susceptibility, and thus is grounds for terminating the patient's employment in the plant. With simple local treatment and prevention of further exposure, the eruption clears up completely within a week

CLINICAL MANIFESTATIONS

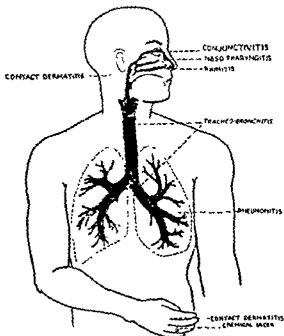


FIG. 2 Diagram of the pathologically affected areas in workers engaged in extracting beryllium from beryl

Chemical conjunctivitis usually, though *not* always, accompanies the contact dermatitis In some instances it has occurred alone. It is not unlike conjunctivitis due to various other types of irritants

The infrequent corneal burn is identical to that seen in "splash burns" by ordinary acids or alkalis

The third dermal change, the ulcer, has occurred in a number of instances at the site of an antecedent abrasion, usually on or near a

knuckle, as shown in Plate I (B). The ulcer has a flat base, and is chronic and relatively painless It may persist for a number of months, until surgically treated by curettage of a pearly-appearing core from within its base, but after such treatment it promptly heals. Histologic study of such cores and also of tissue from totally excised ulcers has



Fig 3 Chest roentgenogram of the first worker to die of acute pneumonitis, in 1940 It exhibits extensive infiltration of both lungs.

revealed evidence of a subacute or chronic type of response to a foreign body, but the specific cause has not been demonstrated microscopically

Although the point may be of academic interest only, in the respiratory cases each of our group of five physicians independently has recognized varying degrees of illness, the mildest being manifested merely by rhinitis, and the most severe by pneumonitis Usually, though not always, the disease of the nasopharynx or of the entire upper respiratory tract has progressed toward pneumonitis if the patient was permitted to con-

tinue in employment in the plant. As in the pneumonitis cases, in the cases of milder respiratory disease affecting the nasal mucous membrane and the pharynx, trachea, and bronchi, the absence of signs of primary inflammatory disease is striking. The membranes are markedly congested and tend to fissure and to bleed easily. Bronchoscopic examinations of



4. Roentgenogram of an 18-year-old boy who had been employed for 38 days in the beryllium-copper department of an extraction plant, and who died on the nineteenth day of his illness. Diffuse infiltration is prominent in the midthird of both lung fields.

several patients showed varying degrees of irritation, from mild to severe, of a type suggesting an external irritant. In the severe form, patchy ulceration was seen.

Usually the patients with the milder forms of respiratory disease become subjectively symptom-free, with an objective return to normal, within one or two weeks after the cessation of exposure. A few patients,

however, continued to have trouble for a number of weeks, although their roentgenograms showed no pneumonic changes.

The manifestation we most fear is the acute pneumonitis. For several years weekly determinations of vital capacity have been made with all workers in both plants Experience has shown that these tests establish

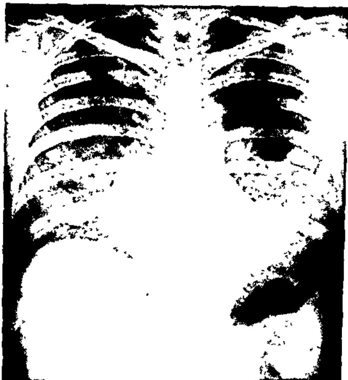


FIG 5 Early roentgenologic abnormalities seen in acute pneumonitis in a 42-year-old chemist The lower third of both lung fields exhibits diffuse infiltration

a fairly stable base line for each worker, and that when a worker's vital capacity begins to drop below his individual base figure, it is time to be concerned At about this time or soon after, the worker begins to note a dry cough, a substernal burning sensation, and slowly but steadily increasing shortness of breath He may complain also of a metallic taste in his mouth He usually but not always observes some decrease in his appetite and some loss of weight. As his illness progresses, his cough may

become slightly productive, usually small amounts of bright red blood are expectorated Weakness and fatigue increase

Without exception, these symptoms always precede the abnormalities observed roentgenologically, the latter appearing usually three or four weeks later By the time roentgenologic evidence of pneumonitis is

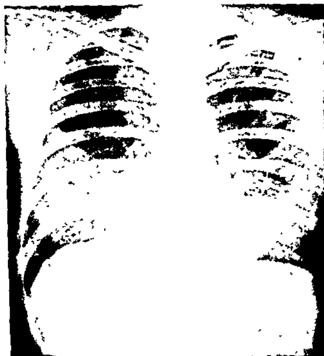


Fig 6 Roentgenogram of the same patient as in fig 5, made a few days later By comparison very little change is noted The patient died about three weeks later.

apparent, the patient's respiration is rapid even when he is at rest, his vital capacity is greatly reduced, and some degree of cyanosis is seen Even at this stage, however, the physical signs found over the lungs may still be very meager Later, when the pneumonitis has progressed further, scattered, sibilant, inspiratory rhonchi and fine to medium râles, particularly prominent in the lower lung fields, are heard on both sides The temperature is usually normal or only slightly elevated Leukocytosis is usually absent

The earliest roentgenologic change is a slight haziness at both lower hilar areas, extending toward the bases of the lungs Within a few days or a week this diffuse bilateral haziness spreads symmetrically over the whole lung During this stage the patient's clinical course becomes more stormy, his respiration is rapid and shallow and he shows varying degrees



Fig 7. Lung tissue from the case illustrated in figs 5 and 6 The patient died on the twenty-eighth day of his illness Note the edematous precipitate filling the air spaces, the small number of polymorphonuclear cells, and the lack of organization

of general cyanosis After the peak of the illness is reached and as clinical improvement begins, the roentgenologic abnormalities begin to clear up, irregular, soft-appearing infiltration is seen. With further improvement, discrete, disseminated, rather small nodules or conglomerate lesions appear. Almost invariably the roentgenologic picture returns to normal before all the symptoms abate In the more severe cases the total duration of roentgenologic abnormalities is from four to six weeks on the average The longest time between the onset of symptoms and complete objective and subjective recovery has been 120 days

In summary Our observation has been that in the acute pneumonitis the subjective symptoms consist of: (1) progressive cough, with oc-

casional blood-streaked sputum, (2) progressive dyspnea, (3) substernal burning pain, (4) anorexia, and (5) weakness and fatigue. The objective signs are (1) loss of weight, (2) rapid respiration, (3) reduced vital capacity, (4) cyanosis, (5) hyperemia of the nasopharynx and tracheobronchial tree, and (6) fine to medium sibilant râles, most noticeable in

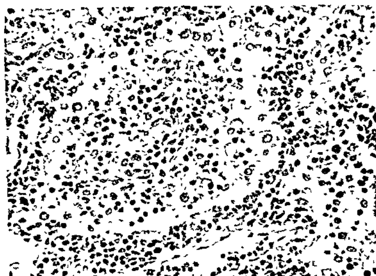


FIG. 8 Lung tissue from a 48-year-old man who had worked in the beryllium-copper department of the plant for 10 months, and who died of acute pneumonitis after 42 days of illness In this case clinical and pathologic examination revealed superimposed bacterial pneumonia The section shows pathologic changes compatible with both conditions. There is an accumulation of large mononuclear cells, lymphocytes, and an occasional polymorphonuclear leukocyte in the alveolar wall and spaces

the lower lung fields The temperature is normal or only slightly elevated, and the clinical laboratory findings are essentially within normal limits. The roentgenologic signs invariably are delayed until three or four weeks after the onset of symptoms, and vary with the stage and severity of the disease In the order in which they appear, they consist of. (1) diffuse bilateral haziness, (2) irregular soft-appearing infiltration, and (3) discrete or conglomerate nodules The roentgenologic picture returns to normal before the subsidence of the symptoms.

Almost all the patients who had acute pneumonitis and recovered

have been followed up, and so far they show no evidence of residual disease, their vital capacities and roentgenograms being normal.

Postmortem examinations were made of 5 of the 6 patients who succumbed The observations were essentially negative except for the lung disease and for acute cor pulmonale The dominant histologic feature



Fig. 9. Section of tissue from a different area of the lung, in the same case (fig 8) Fewer polymorphonuclear cells are present

of the lungs was pronounced intra-alveolar interstitial edema, along with varying degrees of organization. The pathologist of the Cleveland Clinic has commented on the similarity of the histologic picture to that in the cases of phosgene poisoning which he encountered in World War I, and also to that in the fatal cases of poisoning by nitrogen oxide in our disaster at the Cleveland Clinic.

The accompanying illustrations show the roentgenologic and histologic patterns Figure 3 is a chest roentgenogram of the first pneumonitis patient, who died in 1940. The film is a rather poor one made with portable apparatus when the patient was critically ill Figure 4 is a roentgenogram of an 18-year-old boy who had been employed for only 38 days in the beryllium-copper department of the plant, and who died after only 19 days of illness

The early roentgenologic signs in a 42-year-old chemist are shown in fig 5 Although little further change is shown in fig 6, made a few days later, the patient soon died, after an illness of only 28 days The histologic specimen (fig 7) from this case illustrates advanced pulmonary edema The polymorphonuclear cells are few, and in this instance little

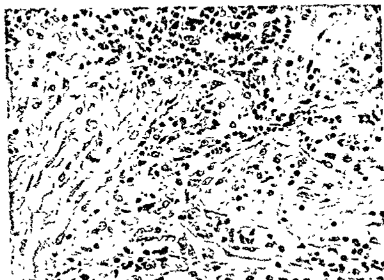


FIG 10 Another section of lung tissue from the same case (figs. 8 and 9) This specimen shows the infrequent polymorphonuclear cells and the thickened alveolar walls which are also characteristic of acute pneumonitis

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Figure 8 is a photomicrograph of lung tissue from a 48-year-old man who had worked in the beryllium-copper department for 10 months before the onset of his symptoms, and who died after 42 days of illness In this case the roentgenograms did not show the usual symmetrical distribution of the lesions, and the presence of superimposed bacterial pneumonia was recognized The postmortem microscopic examination, however, revealed the same fundamental pathologic condition as in the other fatal cases, with thickening of the intra-alveolar walls and with

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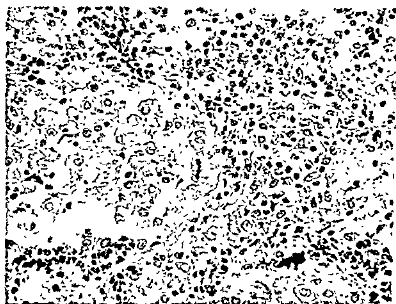


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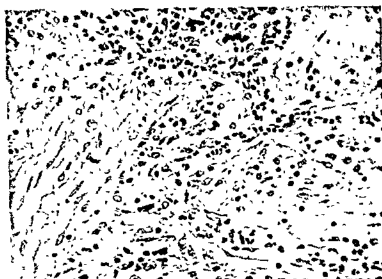


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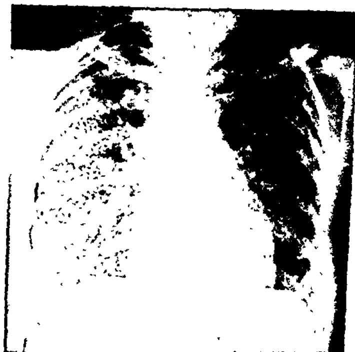


FIG 11. Disseminated nodulation occurring in acute pneumonitis after the peak of illness has passed and recovery is beginning. This patient, a woman, had been employed for 2 months in the melting department of an extraction plant A roentgenogram made 2 weeks later showed the lungs to be completely clear.

same case, and illustrates an increase in the number of plasma cells, a not uncommon phenomenon in these cases. Figure 10, again from the same case, shows an area of greater organization.

The roentgenogram in fig. 11 illustrates the stage of disseminated nodulation after the peak of illness had been passed and the symptoms were beginning to abate The patient in this case was a woman who had been employed for two months in the melting department before the onset of her symptoms, and who made a complete clinical recovery

Figure 12 is a microscopic study of lung tissue from a 35-year-old woman who had been employed for only six weeks in the grinding department before the onset of her symptoms, and who was ill for only 21 days before her death. Dr. Leroy Gardner thought that this specimen showed the most marked degree of organization seen in any of our



FIG. 12. Lung tissue from a 35-year-old woman who had been employed for 6 weeks in the grinding department of the plant, and who died of acute pneumonitis on the twenty-first day of illness. In Dr. Leroy Gardner's opinion, this specimen showed the most marked degree of organization seen in the 5 fatal cases of acute pneumonitis in which autopsies were performed. He believed that in this case chronic irreversible pathologic changes would have occurred if the patient had survived.

cases. This was the only case in which he believed that chronic irreversible changes would have occurred if the patient had not succumbed.

Treatment and Prevention

Although various therapeutic measures have been tried, no specific has yet been found. In the pneumonitis cases our treatment has been supportive, and we have found the most important measures to be: (1) early prevention of further exposure, when the vital capacity begins to drop below the individual's established base level, (2) early absolute

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rest, and (3) oxygen. Benadryl or pyribenzamine, though not consistently helpful in this type of pneumonitis, are considered beneficial in the dermatitis and milder respiratory disease, despite the fact that allergy studies of a small group of patients recovered from various types of beryllium poisoning gave results which could not be correlated in any way.

The companies, with the cooperation of everyone concerned, have accomplished much in the way of prevention by means of improved ventilation, and of measures to prevent accumulation of dust, and by the use of shields for furnaces and of gas masks and respirator masks for the employees. We believe that the periodic tests of the employees' vital capacities have reduced the incidence of severe cases of disease, despite the fact that the number of employees exposed has steadily increased. Until completely effective preventive measures are devised, however, more effective methods of treatment are needed.

Discussion

M. G. CARMODY, M.D.*

I believe there is little that can be added to what Dr. VanOrdstrand said about acute beryllium poisoning, except for a few words to emphasize the fact that new cases are still appearing, especially of the acute chemical pneumonitis, which is one of the most severe forms of this industrial disease. In spite of our efforts to eliminate all dust and fumes, and of the institution of general house-cleaning measures, the incidence of chemical pneumonitis does not seem to have decreased very much The reasons for this are: (1) an increase in the production of beryllium in these plants, and (2) a decrease in efficiency, due to the fact that local rumors of disease in the plants have forced the employers to accept less efficient types of workers than were formerly available.

A brief discussion of some unusual features of the two latest cases of pneumonitis occurring in the Painesville plant may be of interest.

One case was that of a white male 20 years of age who was admitted to the hospital on March 25, 1947. Three weeks before admission he had developed laryngitis, and then gradually had developed shortness of

* Medical Consultant, Clifton Products Company, Painesville, Ohio

breath and, as he put it, "bouts of fever" His temperature on admission was 38° C., but in 12 hours it rose to 40° C. During the course of his illness his temperature varied, reaching 41° C at one time. This fact is mentioned because in most of our cases of acute chemical pneumonitis, fever when present is of low grade. Chills are not usually associated with this entity. The chills and fever in this particular case were considered results of a concurrent infection They were controlled moderately well with large doses of penicillin

On several occasions this patient's respiratory rate rose as high as 85 per minute, illustrating the extreme respiratory embarrassment which accompanies acute chemical pneumonitis

Not to be outdone in his unusualness, two days before his death this same patient developed a spontaneous pneumothorax on the left side Roentgenologic examination revealed a complete collapse of the left lung It is well known that spontaneous pneumothorax may occur in a number of pulmonary diseases such as cancer, tuberculosis, abscess, emphysematous conditions, pneumonias, and traumatic lesions, but as far as I know this is the first case in which spontaneous pneumothorax complicated acute chemical pneumonitis It probably resulted in this instance from the rupture of an emphysematous bleb

In the other case the continuous inhalation of a mixture of 5 parts of oxygen to 2 parts of helium seemed to ease the respiratory embarrassment considerably It is well known that mixtures of helium and oxygen have been used in severe seizures of bronchial asthma The helium molecule, being much lighter than the oxygen molecule, carries the latter with it into the alveoli, thus permitting greater oxygenation of the blood than would otherwise occur The moderate relief achieved in this case by this means suggests that in this disease bronchiolar spasm and obstruction occur, probably in association with pulmonary edema The same line of thought leads to the idea that the patients develop allergic reactions to the products of their disease, it is not unlikely that the use of antihistamine drugs may give encouraging results

Since the publication of our preliminary report on chemical pneumonitis in 1943,[623] thousands of dollars and thousands of hours have been spent by interested physicians, research workers, and institutions in efforts to discover the agent or agents which cause disease in people working with beryllium I for one cannot help thinking that if the

patients and the laboratories were closer together, the study of these diseases would be facilitated and that therefore the causative factors would be more readily exposed.

Further Discussion

DR. HARRINGTON *I should like to ask Dr. VanOrdstrand whether, when* he referred to the beryllium-copper department in a certain unnamed company in a certain unnamed state—I assume it is Ohio—he did not refer to the division manufacturing beryllium-copper master alloy by electrolysis, by means of a fluoride bath? And may I make a strong plea that statements of that kind be amplified to help us discover the specific conditions leading to illness? One case originated in a grinding room What was being ground? It should be possible to obtain from the company's files some information on the conditions under which the employee worked.

DR. VANORDSTRAND I left out such information because it is given by other members of the symposium The plant is that of the Brush Beryllium Company in Lorain, Ohio.

You are right about the beryllium-copper work. The matter of the grinding room has never been too clear to me, and so I shall refer that question to Dr. Zielinski

DR ZIELINSKI Dr. Harrington, I don't quite understand the last part of your first question. Did you mention a fluoride bath? As far as the beryllium-copper is concerned, no fluoride is involved.

DR. HARRINGTON. A fluoride bath is used in one method of making the master alloy These details are important

DR ZIELINSKI. In the grinding room the exposure did not result from the woman's occupation as a grinder of heat-treated ore, but the dispersion of a specific heavy fume from a mill in the same room The mill is used in the sulfating of this ore.

DR HARRINGTON: You understand why I asked. That information is going to help us to keep clear on what is going on We know now that an alloy was not responsible in that particular case.

DR AGATE: People have been asking me what our experience has been on the other side of the Atlantic I must admit that it has been very

limited. I have seen all the people who have worked in one extraction plant, that is, about 36 men In this group 2 cases occurred which somewhat resembled your pneumonitis cases. One patient had a mild pneumonitis. The other probably had only tracheobronchitis, but I cannot vouch for that, not having seen him at the time of his attack The roentgenograms in the more severe case showed a fine stippling in the bases and mid-zones of both lungs

Apparently, we have had no cases of chronic or delayed pneumonitis so far I must qualify my remark by explaining that, though exposure to beryllium compounds undoubtedly takes place in the United Kingdom, certain requirements of security have had to be observed, and I have not yet been able to ascertain to my own satisfaction that no cases have occurred Clearly, one cannot make such a claim until one has looked for such cases I have learned enough in this symposium to realize that I must continue to search most carefully when I return to England

As for dermatitis, in our experience it frequently occurs in beryllium-extracting plants. As a fluoride process is used, the fluoride, at least until recently, has been considered more responsible than the metallic ion But I have been engaged in work in an aluminum-reduction plant where quantities of fluoride are evolved from cryolite flux, and no cases of dermatitis were to be seen

We have had 1 case of acute nasopharyngitis in a man who inhaled the dust of beryl ore during grinding

DR VANORDSTRAND For some time Dr DeNardi and Dr Carmody have been using penicillin as a matter of routine in their cases of acute pneumonitis That treatment is primarily prophylactic

CHAPTER 7

Acute Pneumonitis in Beryllium Workers With Case Histories

JOSEPH DENARDI, M.D.*

The health problems encountered in the manufacture of beryllium and its compounds and in their use in industry have received widespread attention since 1940 Because beryllium has valuable properties, it has come to be used extensively in a number of industrial fields With increased production and use of the metal and its inorganic compounds, acute dermal manifestations of poisoning, and respiratory syndromes varying in the time of onset, have appeared among industrial workers Only the acute dermal and respiratory manifestations have been encountered in the two plants under my direct medical supervision. The chronic, delayed type of pneumonitis has been reported mainly in employees engaged in handling the phosphors used in fluorescent lamps Several neighborhood cases are under study at present, and in these cases the clinical and pathologic picture is closely similar to that in the chronic type of pneumonitis reported by Dr Hardy and Dr. Tabershaw.[291]

Since my associates and I published our report on beryllium poisoning in 1945,[620] a series of new cases has been added to those already reported Between 1940 and December 1, 1947,† I personally observed 315 cases of poisoning among workers in the two plants, which produce beryllium and various compounds and alloys. Dermal manifestations occurred in 163 cases, and major respiratory manifestations in 152 cases. In 117 cases of dermatitis there was definite evidence that host-sensitivity as well as contact was an etiologic factor, 44 cases were due to direct contact, and 2 cases were unclassified Of the 152 patients with major

* Consultant, Brush Beryllium Company, Lorain, Ohio
† The paper as given at the Sixth Saranac Symposium has been revised to include additional cases, up to December 1, 1947 (Ed)

disease of the respiratory tract, 109 had tracheobronchitis, and in 43 cases the diagnosis definitely was chemical pneumonitis. Chemical nasopharyngitis preceded the tracheobronchitis or pneumonitis in the majority of cases, but often occurred as an entity. Because of the mildness of the nasopharyngitis, which was not disabling, no accurate data was obtained The dermal manifestations may be urticarial or hyperemic lesions, discrete papular lesions, a combination of papular and vesicular lesions, or the so-called beryllium ulcers Usually the lesions are confined to the exposed parts of the body, but in many cases of relative hypersensitivity they are widely distributed and urticarial in nature.

Unquestionably, individual sensitivity is a definite factor in determining the time when the dermatitis appears, and its extent. More than 25 per cent of the new employees coming in contact with the fumes and dusts of the various beryllium salts have developed dermatitis of varying degrees of severity, and suggestive of allergies, on the exposed parts of their bodies In nearly all these cases the dermal manifestations appeared in from 3 to 10 days after employment began—that is, after the initial contact with the beryllium salts The severity and extent of the dermatitis depended on the relative degree of host sensitivity, on the concentration of the offending fumes and dust, and on the duration of contact Mechanical injury to the derma, excessive humidity in the environment, excessive perspiration, failure to cooperate in safety measures, and poor personal hygiene also were recognized as contributing factors We have observed, however, that in spite of all precautions a high percentage of those who have had severe dermatitis develop an identical dermal manifestation if exposed a second time It has been observed also that a high percentage of those who develop dermatitis when first exposed, if they are allowed to continue in the same work invariably develop bronchitis and finally pneumonitis In new employees, therefore, severe dermatitis or a form suggesting allergy is considered an indication of individual susceptibility to pulmonary or bronchial irritation

The various skin conditions associated with the production of beryllium create a rather alarming production problem due to the great loss of manpower Because of the rapid turnover of employees, and because the production of ever-increasing amounts of beryllium has necessitated an increase in the size of the working force, the incidence of dermatitis has not declined

The primary etiologic factors in the dermal conditions are the salts and solutions of beryllium sulfate tetrahydrate, beryllium fluoride, and ammonium beryllium fluoride. It is rather difficult to evaluate the roles played by the element beryllium per se and by the acid radical of the inorganic salts. It may be significant that no skin lesions have been observed in persons handling beryllium metal alone. Probably the dermal lesions in most instances are due to individual sensitivity plus the irritating effects of the acid radical of the inorganic salts. One cannot totally eliminate from consideration, however, the possible effect of beryllium compounds on the skin We are aware not only that metallic beryllium and its compounds have exhibited a number of extreme properties in the fields of chemistry and metallurgy, but also that in the field of physiology the extreme effects of the compounds have been observed with some alarm.

The symptoms in the majority of cases of dermatitis are burning and itching sensations in the affected parts of the body. The treatment consists of the usual antipruritic lotions and ointments During the past six months we have been using antihistamine drugs such as benadryl hydrochloride, and to a limited extent pyribenzamine hydrochloride. The benadryl hydrochloride has been used for both therapeutic and prophylactic purposes, with promising results

The beryllium ulcer usually is acute, but if not properly treated may become chronic. This lesion always is preceded by a dermal abrasion in which small crystals of beryllium fluoride or beryllium sulfate tetrahydrate become imbedded. Contact of the crystals with the tissue fluids by hydrolysis releases the acid radical which destroys the surrounding tissues and produces an ulcer. The tendency is for the surface layer of the skin to heal over the crystalline inclusion and the ulcer crater, and thus to form an indurated papule which undergoes necrosis and finally forms a small abscess Microscopic examination reveals an increase in the number of surrounding epithelial layers and in the number of fibroblasts around the edge of the ulcer—the usual reaction of tissue to a foreign body.

At present the treatment consists of incision of the papule, removal of the crystals if the ulcer is in the acute phase, and curettage of the fibrous base in either the acute or the chronic phase. After such treatment healing by second intention is complete within from 7 to 14 days.

We have been greatly concerned about the incidence of the most severe form of beryllium poisoning, namely, the pneumonitis, and about the mortality in this disease. Three deaths, all occurring in 1943, were reported among the employees of one plant alone Another death, occurring on September 18, 1942, was reported with the questionable diagnosis of "acute gas poisoning due to beryllium oxide." In this case the diagnosis also included: hypertension (the systolic blood pressure had been 204 mm and the diastolic pressure, 140 mm), chronic nephritis, myocardial degeneration with early decompensation The patient, who died rather suddenly, had felt considerable pain in the cardiac region Permission for an autopsy was not granted

The duration of the exposure in our cases varied, and it was not always possible to identify the type of fume or dust causing pneumonitis In general, the incidence and severity of this disease was proportional to the length of exposure and to the irritating quality of the various dusts and fumes associated with processing the ore

Before 1939 there were no cases of beryllium poisoning in local plants, although one plant had been in operation since 1935 In late 1942 and early 1943, however, my associates and I, with a rather meager knowledge of the disease and its treatment, were faced with a relatively large group of cases of pneumonitis It was during this short period that we encountered our fatal cases Since 1943 the incidence has subsided considerably, and the mortality has been reduced to zero

We attribute the reduction in the relative incidence, and the present absence of mortality, to improved working environments, to proper use of safety devices, to intensive program of safety instruction involving each employee, to constant medical vigilance, and also to the addition of a few new drugs in the treatment of the major pulmonary manifestation

Two main types of pneumonitis have been encountered in the two plants a fulminating type due to brief exposures to concentrated fumes or dusts, and an insidious type resulting from continual exposure to fumes or dusts over a relatively long period of time

The fulminating type is less common in occurrence It is usually the result of exposure to anhydrous beryllium sulfate fumes, which are formed during the heat treatment of finely pulverized beryl ore frit with sulfuric acid. The symptoms in this type of pneumonitis appear a few

hours after exposure, and characteristically include spasmodic cough, tightness of the chest with substernal pain, and marked exertional dyspnea. In the severe cases varying degrees of cyanosis are observed The physical examination reveals acrocyanosis, a marked and sudden decrease in the vital capacity, limited expansion of the chest, and squeaky râles of the entire chest, resembling those heard in an asthmatic attack. Recovery in these cases is usually rapid, occurring in from 7 to 16 days if the patient receives adequate medical care.

The insidious type of pneumonitis usually follows prolonged exposure to the fumes or dusts of beryllium sulfate tetrahydrate and beryllium fluoride This condition probably is due to the cumulative irritating effect of small amounts of acid radical in the bronchioles.

In this type of the disease the subjective symptoms, in the order of the frequency of their occurrence, are. dyspnea on mild physical exertion, spasmodic cough, aggravated in the supine position, and in rare instances productive of blood-streaked sputum, substernal pressure or burning pain with tightness of the chest, noted especially on the inspiratory effort, general weakness, anorexia with loss of weight, before treatment The dominant objective findings are a marked drop in the vital capacity, acrocyanosis of varying degrees, depending on the extent of the involvement, fine to coarse inspiratory râles and sibilant rhonchi heard first at the base of each lung and then in the hilar areas, a rapid pulse along with an increased respiratory rate. The temperature is normal except in the presence of secondary infection or of infection in the terminal stages of fatal cases Laboratory examination always reveals a normal blood count and sedimentation rate and normal urine throughout the course of the disease

Roentgenologic changes in the lungs do not occur until one to three weeks after the onset of the disease In the typical case of pneumonitis a punctate type of peribronchial haziness and of infiltration scattered throughout the lower half of each lung field is seen. This particular type of punctate infiltration gives an almost granular appearance, such as is seen in pneumoconiosis and some mycotic conditions. In the severe pneumonitis cases, this punctate infiltration progresses to actual consolidation, producing a "snow flurry" effect sometimes resembling that seen in roentgenograms of malignant metastatic lesions.

Whereas in the fulminating type of pneumonitis, recovery occurs

within a period of one to three weeks, in the insidious type complete recovery may require from 4 to 12 weeks. One of our patients was disabled for 166 days

The treatment of either type of acute pneumonitis is rest in a hospital and the intermittent use, as indicated, of oxygen administered by means of a mask During the past six months, besides oxygen we have been administering penicillin and the antihistamine drugs, with gratifying results in the relief of respiratory dyspnea and spasmodic cough, and perhaps in the shortening of the course of the disease. The bronchial and bronchiolar edema, with the resulting diminution of the blood supply of the area, is an invitation to infection by the pathogens of the respiratory tract Such infection is probably prevented by the prophylactic administration of penicillin The antihistamine drugs probably have the effect of relieving the bronchial and bronchiolar spasm by preventing the reaction, suggestive of allergy, produced either by the primary inorganic irritants, or by the histaminelike products of the reaction of the inorganic salts of beryllium with the body tissues

Acute pneumonitis invariably is preceded by tracheobronchitis, which is either rapid in onset or insidious, depending on the host sensitivity and the type of inorganic irritant. Tracheobronchitis may be the beginning of pneumonitis, or it may exist as an entity When it is an entity, complete recovery in cases under professional care requires from 7 to 28 days.

Table III shows the probable causes and the total time of disability in this series of 315 cases

Case Reports

Eighteen cases of recovery from chemical pneumonitis between 1941 and 1947 are reviewed to show complete resolution of the process without evidence of chronicity or recurrence once the individual was removed from exposure. One patient in this series died early in 1947 of generalized carcinomatosis

Case 1

This young man who was 21 years old at the time of his illness, presented our first known case of pneumonitis originating in the Lorain plant He was first employed on January 15, 1941, on work concerned

hours after exposure, and characteristically include spasmodic cough, tightness of the chest with substernal pain, and marked exertional dyspnea In the severe cases varying degrees of cyanosis are observed. The physical examination reveals acrocyanosis, a marked and sudden decrease in the vital capacity, limited expansion of the chest, and squeaky râles of the entire chest, resembling those heard in an asthmatic attack. Recovery in these cases is usually rapid, occurring in from 7 to 16 days if the patient receives adequate medical care.

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TABLE III MAN-DAYS OF DISABILITY DUE TO VARIOUS DERMAL AND RESPIRATORY MANIFESTATIONS OF BERYLLIUM POISONING

	Pneumonitis				*Bronchitis*				*Dermatitis*				
	Cases probably caused by			*Days of disability*	*Cases probably caused by*			*Days of disability*	*Cases probably caused by hypersensitivity plus contact with*		*Cases probably caused by contact with*		*Days of disability*
	Fluoride	Sulfate	Unidentified substance		Fluoride	Sulfate	Unidentified substance		Fluoride	Sulfate	Fluoride	Sulfate	
1940	—	—	—	—	—	1	—	—	—	—	—	—	—
1941	—	1	1	86	—	1	—	—	—	3	—	—	—
1942	3	3	—	219	3	7	3	81	4	4	1	1	18
1943	1	—	5	162	5	10	9	397	5	5	—	—	71
1944	—	—	5	477	—	5	2	214	5	5	—	1	92
1945	7	—	—	228	9	6	4	578	12	9	4	—	240
1946	2	—	1	232	9	—	2	208	13	—	5	—	132
1947	8	2	4	461	21	5	7	600	44	8	26	6	633
Total	21	6	16	1865	47	35	27	2078	83	34	36	8	1186

with a crystallizing process. He was exposed mainly to dust and fumes of beryllium sulfate

The history of this patient was one of the usual childhood diseases, with no major involvement of the respiratory tract The family history was irrelevant

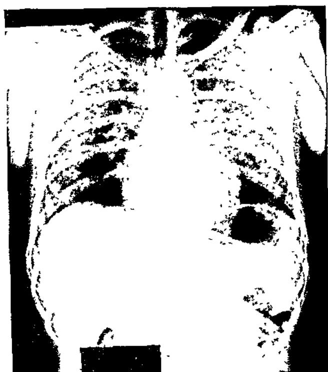


FIG 13 *Case 1, 4-9-41* Diffuse infiltration of both lung fields 24 days after onset

On March 16, 1941, he was suddenly seized with an attack of dyspnea associated with substernal pain and a spasmodic cough, and afterward was confined to bed He had attacks of sweating but no chills He complained of dyspnea induced by talking or bending forward. His cough, which remained spasmodic, occurring at irregular intervals, produced a clear "dust-streaked" sputum Anorexia and general malaise were concomitant symptoms

On his admission to the hospital on March 20, examination revealed the patient to be moderately dyspneic, with definite acrocyanosis Bi-

lateral mild palpebral conjunctivitis was noted The chest expansion was equal on the two sides, but somewhat diminished Fine crepitant râles and sibilant rhonchi were heard in the hilar areas and bases of the lungs The laboratory findings were normal. A chest roentgenogram taken on April 9 is shown in fig 13.

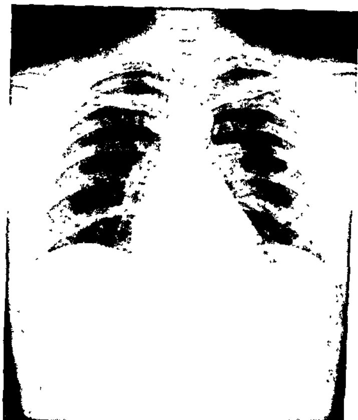


FIG 14 *Case 1, 8-20-47.* Checkup roentgenogram made in Canal Zone reveals complete clearance with no evidence of residue.

During the patient's hospital stay there was slow but definite improvement The pulse and respiratory rates were elevated, but the temperature remained at a normal level He was released on April 29 in excellent condition

Soon after his release this patient joined the armed forces, and in the late summer of 1947 was on active military duty in the Canal Zone. A roentgenologic check-up (fig 14) made in the Canal Zone in August of that year revealed no evidence of recurrence of the disease

Case 2

This man, who was 49 years old at the time of his illness in 1941, recovered completely from acute chemical pneumonitis and returned to work in the plant In September 1947 he was still working in the same environment, in the maintenance department, with no recurrence of the disease in spite of continuous exposure

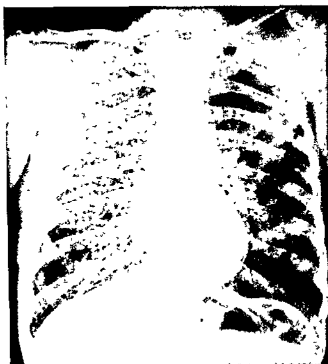


FIG 15 *Case 2, 4-28-41* Diffuse, generalized mottling of both lungs 37 days after onset of symptoms

This patient's personal and family histories included no major respiratory diseases or malignant lesions His pre-employment examination revealed a normal cardiorespiratory system, bilaterally relaxed inguinal rings, and a blood pressure of 150/70 His weight was 122 pounds.

He began working in the plant on February 26, 1941 About 10 days later he developed a papular rash of the face and forearms, and his face became markedly edematous. This condition disappeared in one week without professional care, and without his removal from his working environment One week after the disappearance of the rash, however, he

noticed some dyspnea on exertion, and also weakness and a spasmodic cough, which was aggravated when he was in the supine position. Some blood-streaked sputum was expectorated He complained of hoarseness before the onset of the cough Substernal pain on inspiration followed the early symptoms. The patient developed decided anorexia with nausea, and subsequently lost 12 pounds in weight.

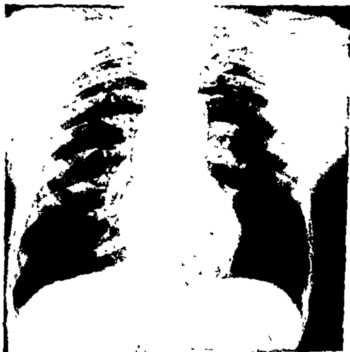


Fig 10. Case 2, 8-26-47. *Patient has worked continuously in plant* since recovery from acute pneumonitis No residual fibrosis or parenchymal involvement noted at present

On April 17 he was admitted to the hospital. Examination revealed the patient's weight to be 114 pounds His face was pale, with some cyanosis of the lips. The expansion of the chest was definitely diminished *There* were many fine crackling râles of both lung bases, and musical râles of the hilar areas The percussion note was resonant throughout the chest. [illegible] stated: "There is a [illegible] xes and bases, [illegible] tory condition of indeterminate character"

The statement that the cause was unknown was proper in this case of

a new and unusual lung condition encountered in an industry which except for Case 1, had been relatively free of major pulmonary disease for more than five years

The patient was discharged from the hospital on April 29, and returned to work on June 1.

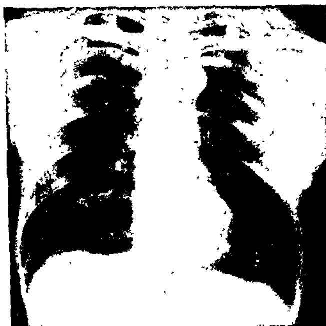


Fig 17 *Case 3, 9-2-47* Tenting of right diaphragm with evidence of some fibrosis of right lower lung No parenchymal involvement at present

When this man was examined on August 26, 1947, he was found to be in excellent physical condition The report of the roentgenologic examination on that date (see fig 16) states "Examination of the chest shows no residual parenchymal changes at this time in either lung. There is no residual fibrosis, and no parenchymal infiltration"

Case 3

The patient, a man then 44 years old, was first employed in the plant on April 13, 1942, in the maintenance department.

The individual and family histories were not obtained, but the patient admitted to immoderate use of alcohol.

On May 21, he was admitted to the hospital in marked dyspneic state. He stated that two days previously he had inhaled concentrated fluoride

fumes, and that a few hours after this exposure he had noticed tightness of the chest, a spasmodic cough, and appreciable shortness of breath When the symptoms became worse he was remanded to the hospital for treatment

The examination on admission revealed the patient to be in respiratory



FIG 18. *Case 4, 12-17-42* Roentgenogram of chest reveals a generalized involvement of both lungs. Second attack of pneumonitis with only 8 days exposure

distress and definitely cyanotic. The temperature was 99 6° F., the pulse 112, and the respiratory rate 60 The chest expansion was markedly diminished, and appreciable dullness of the percussion note was noted over the middle and lower lobes of the right lung Many moist râles with some tubular breathing were heard over the same area, and fine sibilant rhonchi were heard throughout the rest of the chest

The diagnosis at the time was acute fulminating pneumonitis, with secondary lobar pneumonia on the right side

Oxygen and sulfathiazol were given as indicated. The temperature rose to above 104° F on two occasions The respiratory rate ranged between 30 and 60 Gradual improvement occurred, and on June 23 the patient was discharged from the hospital as fully recovered

On September 3, 1947, this patient was interviewed He stated he was in good health and was working seven days each week A report made on September 4, on a final x-ray check-up (fig 17) states·

"Examination of the chest shows a small, pleural adhesion extending from the outer portion of the right dome of the diaphragm, and produc-



FIG 19 *Case 4, 9-6-47.* No evidence of residual parenchymal involvement.

ing some tenting of the diaphragm. There are other prominent peribronchial shadows suggesting residual fibrosis, in the lower right part of the chest. There is no evidence of any parenchymal infiltration at this time. No punctate mottling is seen The left lung is clear

"Impression Residual fibrosis and a pleural adhesion in the lower right part of the chest No evidence of activity at this time"

Case 4

This man was 52 years old at the time of his employment, which began on September 14, 1942. He was assigned to the crystallizing department where he was exposed to beryllium sulfate solution and fumes

No relevant family history was given by the patient, and his own history was negative except for a fractured left hip in 1920 and pertussis in childhood.

The pre-employment examination disclosed no physical abnormalities. The blood pressure was 140/80

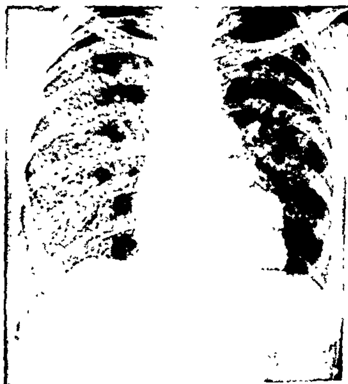


FIG 20 *Case 5, 8-24-43* Appearance of chest 37 days after onset of symptoms. Marked nodular infiltration of both lungs

On October 25 he noticed a spasmodic cough and dyspnea on exertion Subsequently he developed anorexia, with loss of weight.

A chest examination revealed limitation of expansion, and fine wheezy râles of both hilar areas The percussion note was unaltered throughout both sides of the chest Roentgenograms confirmed the diagnosis of pneumonitis.

Symptomatic treatment was given, and recovery was complete The patient returned to work performing the same operation as before, on November 30.

On December 8 he noticed a recurrence of the same symptoms as

before, and was admitted to the hospital on December 12 The physical and roentgenologic findings (see fig 18) were typical of chemical pneumonitis.

Slow improvement occurred, and on December 31 the patient was sufficiently recovered to be discharged On January 11, 1943, completely recovered, he returned to the plant to work in the maintenance department.

This patient was interviewed on September 8, 1947, and stated that he was working on a construction project and was in excellent health

The report on a roentgenologic check-up (fig 19), made on September 6, 1947, reads as follows "Examination of the chest shows a slight accentuation of the bronchovascular markings The lung fields are otherwise clear There is no evidence of any residual pneumonitis"

Case 5

This patient was a woman aged 39 at the time of her employment in the plant She was hired as a furnace operator on June 10, 1943 For eight weeks she worked in the department where beryl ore is melted and at one time helped in the repair of a beryllium fluoride furnace which was adjacent to her station in the plant

On August 7 she presented herself for medical examination, complaining of a shortness of breath, weakness, and a spasmodic cough with a slight streaking of blood in the sputum These symptoms had been progressive for three weeks and during this time she had lost 14 pounds in weight

Her previous history was negative, except for colloid goiter since adolescence.

On August 18 the patient was admitted to the hospital Examination revealed limitation of the chest expansion, marked dyspnea, acrocyanosis The breath sounds were muffled and persistent moist squeaky râles were heard throughout both lungs She complained of substernal pain on inspiration.

Chest roentgenograms (fig 20) showed an atypical nodular infiltration resembling that seen in pneumoconiosis The laboratory findings were within normal limits

The patient's recovery was slo[illegible]

in [illegible]

8, [illegible] l

go

[illegible] 149 pounds [illegible] stated she was in

The report on the final x-ray check-up (fig 21), made on August 21, 1947, states

"Examination of the chest shows a slight accentuation of the broncho-

vascular markings in both inner lung fields There is no evidence of any active pulmonary tuberculosis, and no evidence of any peribronchial pneumonitis There is no enlargement of the heart. The domes of the diaphragm are normal in contour and position. There is no roentgenologic evidence of residual fibrosis or peribronchial changes due to pneumonitis."

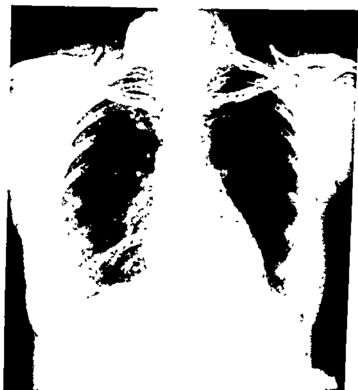


FIG 21. *Case 5, 8-21-47* No evidence of residual of previous pneumonitis

Case 6

This man was 39 years old at the time of his illness, which began after he had been employed in the plant for two weeks He had worked as a pipe fitter in Building II, where no fumes were produced, but where he and his coworkers (see cases 7 and 8) had been exposed to considerable quantities of dust containing beryllium sulfate and beryllium fluoride

His history included the usual childhood diseases, but the patient denied any major illnesses of the cardiorespiratory system. The family history included no pulmonary diseases or malignant lesions.

On January 15, 1944, the patient presented himself for examination,

complaining that during his two weeks in Building H he had noticed shortness of breath on exertion, a nonproductive spasmodic cough, substernal discomfort when he was supine, anorexia, and loss of a few pounds in weight The physical findings and the chest roentgenograms were typical of early pneumonitis



FIG 22 *Case 6, 8-15-47* Accentuated bronchovascular markings noted now but no evidence of parenchymal involvement Chest films at height of disease were identical with those of case 7

This patient was treated symptomatically as an ambulatory case Complete resolution of the pneumonitis was noted about February 11 He was last seen for this illness on March 28, at which time the chest was found to be in a healthy state

On August 15, 1947, he was again examined and found to be in excellent physical condition An x-ray check-up (fig 22) on the same day was reported as follows

"Examination of the chest showed accentuated bronchovascular markings in the lower part of the right lung. There is no evidence of any specific pneumonitis at this time"

Case 7

This man, aged 65 at the time of his illness, like the patients in cases 6 and 8 had been employed as a pipe fitter in Building H.

His previous history and family history are irrelevant

A physical examination at the beginning of his employment revealed no abnormal condition of the heart or lungs.

On January 18, 1944, he presented himself for examination, complaining of shortness of breath, a nonproductive spasmodic cough, weakness,



FIG 23 *Case 7, 2-11-44*· Marked involvement of perihilar and central pulmonic areas

substernal pain on inspiration, and anorexia with some loss of weight. These symptoms had begun approximately on December 25 of the preceding year, and had become so pronounced that he had quit work on January 8.

The physical examination on January 18 revealed definite acrocyanosis, and dyspnea on the slightest exertion There were many musical râles in the hilar and basal areas of the lungs The chest expansion was limited The percussion note was unaltered throughout both sides of the chest

A chest x-ray (fig. 23) made on February 11 revealed early perihilar

pneumonitis. Both clinical and roentgenologic examinations showed that this process progressed until February 25, when the beginning of its resolution was first noted. A chest x-ray made on May 19 revealed complete clearing except for some residual fibrosis

The patient was seen again on August 23, 1947, and was found to be

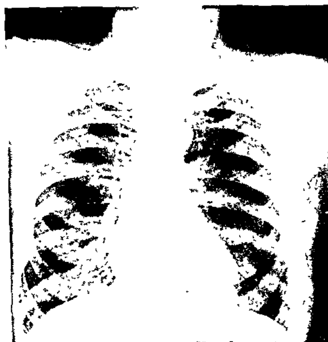


Fig 24 *Case 7, 8-23-47* Suggestive fibrosis of both lower inner lung fields No evidence of parenchymal infiltration

in excellent physical condition The roentgenologic examination (see fig 24), on that date was reported as follows.

"Re-examination of the chest shows linear shadows of a density in both [illegible]

Case 8

This man was 34 years old at the time of his illness Like the patients in cases 6 and 7, he had been a pipe fitter employed in Building H, his employment having begun on December 16, 1943

No relevant history of the individual or his family was obtained

An examination before the onset of his illness had revealed a normal heart and lungs free of any detectable abnormalities

On January 29, 1944, the patient was sent to my office for examination He complained of dyspnea on exertion, of a spasmodic cough with some blood-streaked sputum, of substernal discomfort which became worse



FIG 25. *Case 8, 9-6-47.* Occupation same as case 7. Definite evidence of pulmonary fibrosis is not noted at this time.

when he coughed or when he was supine, and of anorexia with a weight loss of 5 pounds.

The physical examination on that date revealed coarse, musical râles in the hilar and basal areas of the lungs. The chest expansion was less than normal, and produced pain in the substernal area. The percussion note was resonant throughout the chest. Roentgenograms confirmed the clinical diagnosis of chemical pneumonitis. He improved gradually, and on March 24 was free of symptoms He returned to work on April 5, after examination showed complete clearing of the lungs.

A check-up (fig 25) was made on September 6, 1947, and the roentgenologist reported "The chest appears clear at this time No residual pulmonary fibrosis is noted."

Case 9

This patient, a man 47 years old at the time of his illness, was employed in the maintenance department, his employment beginning on March 2, 1944 His specific work was building and rebuilding gas-fired reduction furnaces in all departments, but he worked principally in the beryllium metal department He was exposed to dusts of copper oxide, beryllium oxide, beryllium fluoride, magnesium fluoride, beryllium sulfate, and carbonaceous cement

His history included no respiratory disease, and the family history included no chronic respiratory or malignant disease

On April 5 the patient reported for examination stating that since March 29 he had had a "bad cold" with an intermittent productive cough and a general feeling of weakness, and that all these symptoms had grown progressively worse

He stated that the acrid odors given off by the carbonaceous cements used in the rebuilding of furnace linings had annoyed him, and had caused a rather sudden and decided loss of appetite. The possibility of a toxic agent in the cement was investigated, but the results of the analysis were negative The examination made of this patient's chest on April 5 revealed no unusual condition associated with the industry

On April 12 he complained of intermittent spasmodic cough, general weakness, substernal pain, and dyspnea on exertion, all persisting since April 3 It was learned that 10 days before April 3 the patient had been rebuilding the furnace used for the reduction of ammonium beryllium fluoride

The examination on April 12 revealed appreciable dyspnea and some acrocyanosis The chest expansion was definitely less than normal Coarse moist râles were audible from the rear over the base of each lung Substernal pain was produced by deep inspiration

The patient was treated symptomatically, and on May 15 returned to the same type of work

Within 10 days the symptoms recurred The findings on physical examination were the same as before, and the recurrence of pneumonitis was verified roentgenologically This time the patient was disabled from May 25 to September 21, but clinical and roentgenologic evidence indicated complete recovery In April 1947 this patient was under my care for lobar pneumonia He has been in good health since then, except for a chronic nonproductive cough

The report of an x-ray examination (fig 26) on August 26, 1947, states

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out these areas slight and perhaps questionable parenchymal fibrosis is observed in each lower lung field These changes suggest residual fibrosis due to the past pneumonia or pneumonitis. There are no indications of an active process at this time.

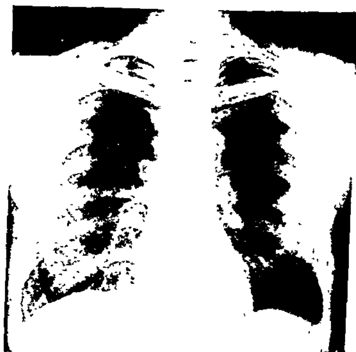


FIG 26. *Case 9, 8-26-47.* No definite evidence of parenchymal involvement. Patient had two attacks of pneumonitis in 1944. Check-up roentgenogram revealed peribronchial fibrosis throughout both lower lung fields

"Impression residual postinflammatory fibrosis in the lower part of both lungs"

Case 10

This man, who was 47 years old at the time of his illness, was first employed in the plant on September 22, 1944 He worked as a mixer in the beryllium copper department and as a furnace operator's helper at the beryl furnace His exposure was mainly to dusts of beryllium oxide, graphite, and elemental copper, and to fumes of reduced silicates. The effects in this case were insidious.

The individual and family history is irrelevant The pre-employment examination failed to reveal any abnormal condition of the cardiac and respiratory systems.

On or about November 14 he first complained of a "chest cold" associated with a spasmodic cough, dyspnea on exertion, and substernal pain when he was in the supine position These symptoms were progressively

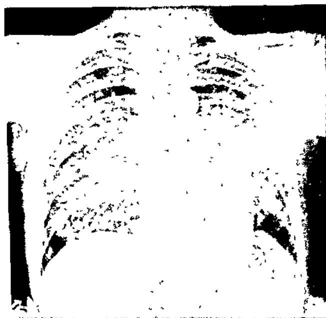


Fig 27 *Case 10, 12-9-44* Pneumonitis involving the hilar and central pulmonary areas, 25 days following onset of disease

aggravated, and he was sent to my office for examination and treatment

The findings on physical examination of the chest were typical of [illegible] ally [illegible] He spent most of his time at a cafe in the neighborhood of his rooming house and there was evidence that he was more than a moderate drinker of alcohol

Despite his aversion to medical treatment, this man made a complete recovery Although his symptoms became progressively worse up to December 10, thereafter there was gradual improvement All laboratory findings were normal The patient was clinically free of symptoms or signs

on March 26, 1945, the day of his discharge. A roentgenogram (fig 28) taken on February 10 revealed complete resolution of the pneumonitis

On January 14, 1947, I was called in consultation to the local hospital, and again saw this man His recent history then was one of abdominal distention and jaundice of several months' duration.

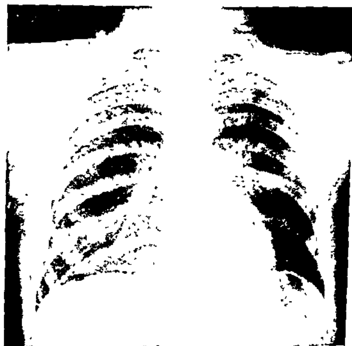


FIG 28 *Case 10, 2-10-45* Pneumonitis has cleared except for slight hilar residue Patient is clinically fully recovered.

Examination showed him to be decidedly jaundiced, poorly nourished, and in a state of respiratory distress. The chest expansion was poor. Coarse, moist râles were heard at the bases of the lungs The percussion note was relatively dull throughout the chest. The abdomen was distended, and signs of a fluid level could be elicited. The liver edge was three inches below the costal margin. An irregular, nodular, firm mass was discovered in the region of the right kidney and ascending colon. Rectal examination revealed a firm, irregular, nodular mass in the cul-de-sac, which was moderately tender.

The roentgenograms of the lungs (fig. 29) made on this date were described as follows·

"Multiple oval opacities scattered throughout both lung fields are noted No evidence is seen of surrounding pneumonitis The shadows in no way

suggest lobar or lobular distribution, and seem to cross the interlobar fissures"

The clinical diagnosis was probable hypernephroma of the right kidney, with hepatic and pulmonary metastases.

The patient was sent to a veterans' hospital, where he died on February 3 At autopsy the final diagnosis was generalized carcinomatosis with many pulmonary metastases.



FIG. 29. *Case 10, 1-14-47* Multiple oval opacities scattered throughout both lung fields The shadows cross interlobar fissures and are very suggestive of metastatic tumor nodules

Case 11

This patient, a man then 39 years of age, was first employed in the plant on March 27, 1945. Working as a furnace tender, he was exposed to beryllium fluoride

The family history and previous individual history are irrelevant

On June 1 this patient complained of a spasmodic cough, dyspnea on exertion, and substernal pain felt on inspiration and aggravated when he assumed the supine position He had lost 6 pounds since the onset of his illness 10 days previously

Because the symptoms became more pronounced, he was admitted to the hospital on June 4. The vital capacity then was down to 76 per cent of normal

Examination revealed limited expansion of the chest, and many fine, squeaky râles in the hilar areas of the lungs. Mild acrocyanosis was noted

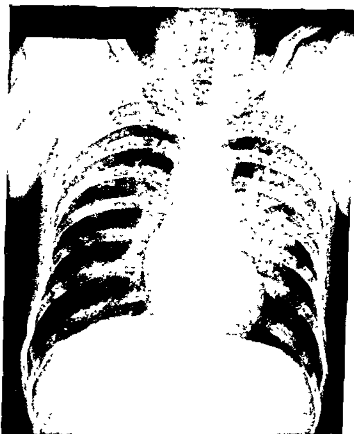


Fig 30 Case 11, 6-13-45 Pneumonitis 23 days after onset of symptoms Process is mainly in the perihilar areas of the lungs

Roentgenologic examination (see fig. 30) confirmed the diagnosis of *pneumonitis*

During his stay in the hospital his temperature remained normal. The laboratory findings were normal.

The patient was discharged from the hospital on June 18 His recovery was complete, without any complication

This man was examined on August 16, 1947, and was found to be in

excellent physical condition. The report of the roentgenogram (fig 31) taken on this date reads as follows.

"Examination of the chest shows no residual fibrotic changes in either lung The bronchovascular markings are not accentuated There is no evidence of any pneumonitis The chest appears healthy at this time."

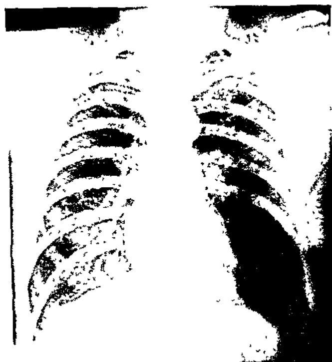


FIG 31 *Case 11, 8-16-47* No evidence of parenchymal involvement Patient is fully recovered

Case 12

This young man, then aged 21, was first employed at the plant on April 16, 1945, as a furnace operator From July 5 to 10 he had a special assignment concerned with the production of aluminum-beryllium master alloy, in the beryllium metal department

His past history and family history are irrelevant

On July 11 this employee complained of substernal discomfort, of spasmodic attacks of nonproductive coughing, of shortness of breath, of anorexia, and of weakness, all of 24 hours' duration.

In an examination on July 13 fine, wheezy râles were heard on both

sides of the chest Limited chest expansion, shortness of breath, a spasmodic cough, and some acrocyanosis were noted.

Roentgenologic examination of the chest on July 23 (see fig. 32) revealed changes typical of chemical pneumonitis, and also showed partial atelectasis of the left lung Another examination on August 3 showed that the pneumonitis was beginning to clear up



FIG. 32 *Case 12, 7-23-45* Onset of symptoms 13 days before The pneumonitis involves the central lung areas.

The patient was treated symptomatically He was frequently seen in the office, as he had an aversion to confinement in a hospital The cough and dyspnea gradually decreased during a period of six weeks He was in excellent physical condition on September 4, when he was discharged from medical care

On August 25, 1947, he was examined and found to be in excellent physical condition The report of the x-ray check-up (fig 33) on that date states

"Examination of the chest shows no parenchymal infiltration at this time. The bronchovascular markings are not unusually accentuated The peripheral lung fields are clear. This is a healthy-appearing chest"

Case 13

This young man, then 21 years old, was employed on September 22, 1946, as a metal worker in the attrition mill

His past history was essentially negative His mother had died at the age of 56 of thyrotoxicosis, but otherwise the family history is irrelevant

A pre-employment roentgenogram showed his chest to be essentially normal His standard vital capacity was 102 per cent

On November 22 the patient presented himself for examination His vital capacity then was 102 per cent There was physical evidence of con-

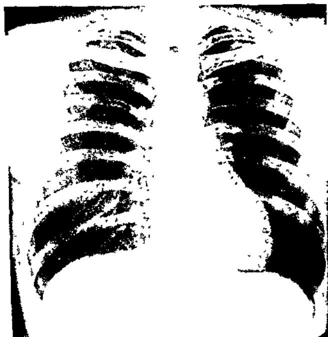


FIG 33 *Case 12, 8-25-47* Patient is clinically well Chest is clear and there is no residue of pneumonitis

siderable metal dust on the mucous membranes of the nose and throat The chest was clear to auscultation He complained of a substernal sensation of burning and pressure, first noticed about three days previously. This was associated with a spasmodic nonproductive cough, worse when the patient was in a supine position He stated that for the previous 24 hours he had had a tendency to shortness of breath on relatively mild *exertion, and that for the previous five days he had had a feeling* of lassitude and general malaise, with definite anorexia

On November 27 he was permitted to return to routine duties. At the next weekly routine check, however, on November 29, although his nose, throat, and chest were found to be clear, his vital capacity was found to

have dropped abruptly to 90 per cent. He was immediately stopped from further work

A physical examination on December 7 revealed the typical signs of pneumonitis. Roentgenograms of the lungs (fig 34) confirmed the diagnosis.



FIG 34. *Case 13, 12-21-46* Moderate pneumonitis of both lungs First symptoms were noted November 19 of same year.

The patient was not hospitalized, but was placed under frequent medical observation. The treatment was symptomatic Serial roentgenograms of the chest showed the pneumonitis proceeding slowly toward resolution

On March 24, 1947 the patient showed clinical evidence of full recovery and his roentgenogram (fig 35) revealed complete resolution of the pneumonitis

Case 14

This young man was 27 years old at the time of his employment in the plant He was hired on October 18, 1946, to work in the attrition mill

His previous history and the family history were essentially negative. A pre-employment roentgenogram (fig 36) showed his chest to be normal. His standard vital capacity was 117 per cent

On the evening of December 26 the patient went to bed feeling and looking apparently well, but the next morning was aroused out of a sound

sleep by an attack of acute dyspnea, with audible wheezing breathing This acute attack, which lasted about 30 minutes, was accompanied by nausea, but not by emesis The acute respiratory symptoms rapidly subsided, but the young man noticed a general feeling of weakness and a decided tendency toward "dizziness" The acute symptoms were given

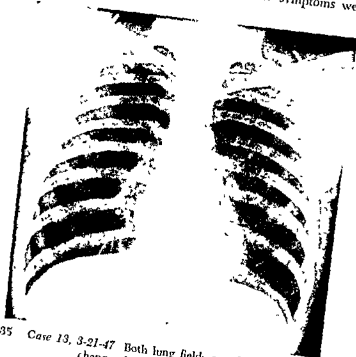


FIG 35 *Case 13, 3-21-47* Both lung fields are clear with no residual changes from the pneumonitis

temporary attention by a neighborhood physician, and on January 4, 1947, the patient made himself available to me for observation and treatment An examination of his chest on this date failed to reveal any objective evidence of pulmonary disease.

On January 11 he complained of shortness of breath, of spasmodic, nonproductive cough, of substernal discomfort felt on inspiration and when he was in the supine position, and of anorexia with an appreciable loss of weight.

The physical examination on this date revealed definite evidence of pulmonary disease The chest expansion was definitely restricted The percussion note was resonant throughout the chest, but fine, crackling, wheezy râles were heard throughout the bases and hilar areas of both

lungs. A roentgenogram (fig. 37) taken at this time revealed a marked pneumonitis in both lower lung fields

The objective symptoms progressively worsened until January 31, but two weeks later there was definite subjective and objective improvement. On April 19 the patient was clinically found to be well, the chest was

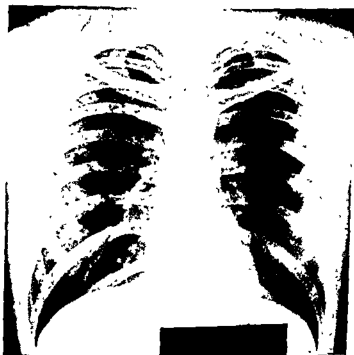


FIG. 36 *Case 14, 10-18-46.* Pre-employment chest roentgenogram revealing essentially normal chest findings.

clear on auscultation and percussion. Roentgenograms (fig 38) revealed a healthy-appearing chest.

When contacted in November 1947 the patient stated that he was in excellent condition and free of all respiratory symptoms.

Case 15

This man, aged 61 at the time of his illness, was first employed at the plant on October 6, 1946, as a carbon lathe operator

His parents had died in the sixth and eighth decades of life of unknown causes He had no knowledge of pulmonary or malignant disease in his family. His own history included the usual childhood diseases. He had been operated on for a ruptured appendix about 20 years before 1946, but had had no other serious illness

On January 8, 1947, he presented himself for medical examination, complaining of shortness of breath, of substernal soreness on inspiration, and of anorexia and loss of weight.

Examination revealed rapid, shallow breathing, and marked acrocyanosis. The percussion note was dull throughout both lungs Fine, dry, wheezy râles were heard throughout both sides of the chest



FIG 37 *Case 14, 1-13-47* Marked pneumonitis in both lower lung fields 16 days after onset of symptoms

The patient was admitted to the hospital on January 13, with the typical roentgenologic and clinical signs of chemical pneumonitis Oxygen and penicillin were given in adequate amounts, and within 12 hours a most remarkable improvement in his condition occurred His breathing became deeper and less labored, and the substernal pain had virtually disappeared Afterward oxygen was used only at intervals

The blood count and sedimentation rate were within normal limits, and the urine was found to be normal

The patient's progress was rather rapid in view of the severity of the disease He was released from the hospital on January 28, and returned

to work, in the same department of the plant, on March 17. On March 31, however, the same severe symptoms recurred, with the same findings made on examination. The patient was again hospitalized on April 1.

Again he was given penicillin and oxygen, and again remarkable improvement was noted clinically. There was no appreciable rise in tem-

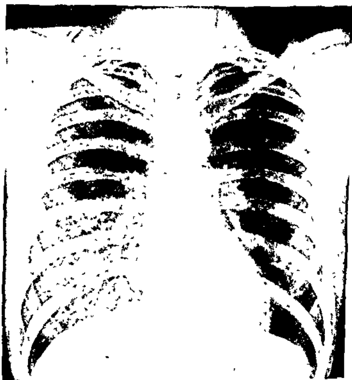


FIG. 38 *Case 14, 4-18-47* No residual pulmonary densities Lung fields are clear.

perature, but the pulse and respiratory rates were above normal. The laboratory findings again were within normal limits. He was released from the hospital on April 12, and on April 28 was discharged from the plant for medical reasons

When interviewed on August 16 this man stated that he was in excellent health and was working every day. The roentgenologic report of that date states,

"Re-examination of the chest shows no unusual accentuation of the hilar or peribronchial markings at this time There is no evidence of any pneumonitis at this time This is a healthy-appearing chest."

Case 16

The patient was an unmarried girl then aged 19, who was first employed at the plant on March 12, 1947, as the operator of a rotary furnace reducing beryllium sulfate to beryllium oxide. On March 27 she was transferred to work with a vibratory separator

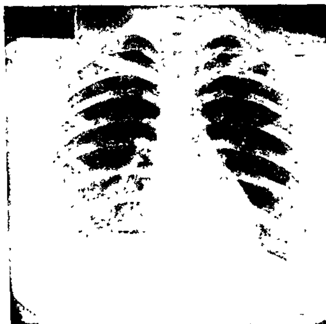


FIG 39 *Case 16, 3-14-47* Pre-employment roentgenogram revealing a normal-appearing chest

The family history was negative, with no tuberculosis or malignant disease The patient's own history also was essentially negative A pre-employment roentgenogram (fig 39) revealed a normal-appearing chest.

Her illness began April 12, with dermatitis of the eyelids This condition cleared in two weeks, but on April 26, the patient complained of considerable spasmodic coughing, of shortness of breath, and of weakness and fatigue, all of one week's duration

On May 26, when the patient was admitted to the hospital, examination revealed definite acrocyanosis, fine musical râles on both sides of the chest, and limitation of the expansion of the chest The percussion note was normal.

The roentgenologic observations (see fig. 40) on that date were as fol-

lows "A rather diffuse nonhomogenous patchy infiltration is seen throughout both lung fields, though apexes remain clear. The diffuse pulmonary infiltration is rather suggestive of chemical pneumonitis"

In the hospital, no penicillin or oxygen was administered. The resolution of the pneumonitis was rather a slow process. The patient was discharged from the hospital on June 18, completely recovered.



FIG 40. *Case 16, 6-26-47* Diffuse, nonhomogeneous patchy infiltration throughout both lung fields. Apexes appear relatively clear

During the hospital stay the temperature was not elevated The cardiac and respiratory rates were moderately increased. The blood count and sedimentation rate remained within normal limits, and the urine was normal.

When interviewed on August 29, the patient stated that she was in good health The report of a roentgenologic examination (fig 41) on that date states

"The lung fields appear clear at this time. There is no evidence of any residual pneumonitis in either lung base *There is no residual fibrosis* This is a healthy-appearing chest."

Case 17

This woman, then aged 33, began work at the plant on January 20, 1947, as a stenographer.

Her personal and family history included no chronic pulmonary dis-

ease or malignant disease In a pre-employment examination the findings were negative. A pre-employment roentgenogram revealed no manifest tuberculosis, calcification of the hilus of the left lung

On May 14, she presented herself for medical examination, complaining of a spasmodic cough, substernal discomfort, shortness of breath, some loss of weight, continual fatigue, and loss of appetite

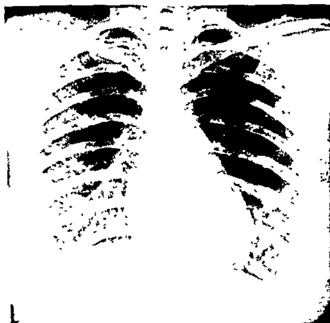


FIG 41. *Case 16, 8-29-47* No evidence of residual pneumonitis or fibrosis.

Examination revealed râles at the base of the right lung, and sibilant rhonchi in the hilar areas of both lungs The chest expansion was decreased Slight acrocyanosis was noted The temperature was slightly elevated

During the entire course of her illness the patient was ambulatory The progress of the pneumonitis was followed by means of serial roentgenograms.

On July 19 the patient was clinically found to be well, and a final roentgenologic check-up on this date was reported as follows. "Re-examination of the chest shows complete clearing of the punctate pneumonitis in both lungs. The lung fields appear clear at this time."

Case 18

This man was 31 years old at the time of his employment in the plant He was hired as an oiler in the maintenance department on January 9, 1947

His family and personal history was essentially negative. A pre-employment roentgenogram (fig. 42) revealed a normal chest

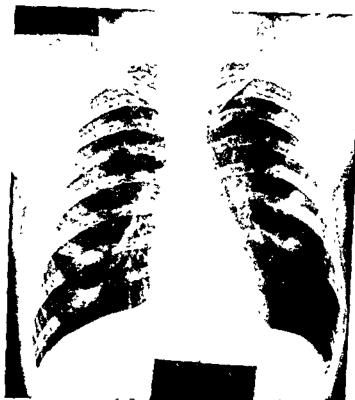


FIG 42 *Case 18, 1-10-46* Pre-employment film revealing a normal chest.

He first complained of substernal pain on inspiration, shortness of breath, and a spasmodic, nonproductive cough on February 22. An examination on this date revealed bilaterally decreased chest expansion The percussion tone was normal, but diffuse wheezing râles throughout the lung fields were heard The patient also had a slight papular rash of the face.

When he
elevation of
squeaky, dry

The râles were most marked at the base of the right lung, and the percussion note was moderately dull over that area Slight acrocyanosis was



Fig 43 *Case 18, 3-17-47* Appearance of chest 23 days after onset of disease Dense, mottled opacities extend from the hila short of the peripheries

xamination, 23 days after the onset of

egative except for strongly positive

The patient was released from the hospital March 24, and returned to work on April 29

When seen on October 7, he was in excellent physical condition His weight was 146½ pounds and his vital capacity was 107 per cent

A roentgenologic examination (fig 44) on October 15 was reported as follows "Re-examination of the chest shows no enlargement of the hilar shadows There is no unusual accentuation of the bronchovascular markings, and no evidence of any peribronchial pneumonitis or punctate in-

filtration at this time. There is no enlargement of the heart. The chest appears healthy, with no residual changes due to pneumonitis"

The patient was examined again on November 26, and was found to be in excellent condition. He stated that he was free of any respiratory symptoms. His vital capacity on November 25 was 120 per cent plus.

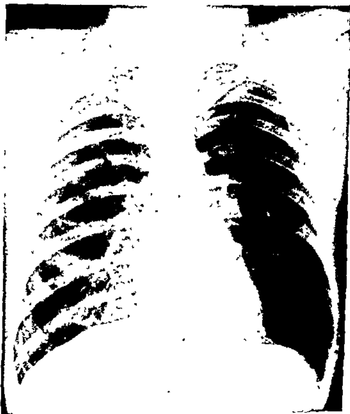


FIG 44 *Case 18, 10-15-47* No residual changes or abnormalities from the pneumonitis Patient in excellent condition

Summary

In the past seven years, among the employees of two plants in the Cleveland area, 315 cases of a disease entity with acute dermal and respiratory manifestations have been encountered The etiology of this disease has not been definitely established. Unlike the condition reported from the fluorescent lamp industry, this illness is not delayed in its onset, and no recurrence has been noted after the patients have been excluded

from the beryllium industry Check-ups of 18 persons who had had severe pneumonitis disclosed no chronic manifestations or recurrence of the disease, and no disability resulting from it

Discussion

CHARLES E. WINDECKER*

The discovery of the health hazards of beryllium production was at first surprising and, of course, alarming I believe the danger was first apparent to producers of beryllium in this country about 1940 or 1941. Undoubtedly, it had been recognized by some people before that time, but in Ohio there was no way of recognizing it at the time of the first outbreak of illness in the industry there With the first cases it became obvious that the patients were suffering from something caused by their employment, but there was no pattern for diagnosis and no pattern for treatment I believe I can give a cross section of the thinking of management by saying that the problem was tackled with the only tools available, that is, by improving working conditions in the plants as rapidly as possible. Working completely in the dark, we have installed dust collection and ventilation apparatus and other safety devices as fast as we could spot the danger points

Throughout industry's experience the trouble has been recurrent and spasmodic In my company's plant an interim of almost two years passed without a single case of dermatitis or pneumonitis From our observations of early outbreaks of the disease, we concluded that the incidence was greatest during winter months, and we attributed the high incidence to the difficulties of simultaneously heating and ventilating the plant. Then the disease occurred in midsummer

We have often considered issuing a paper frankly exposing all our meager knowledge of the problem to our employees, but in each instance have abandoned the idea because our knowledge was insufficient for any type of explanation The fact that we had to leave our employees in the dark as to the degree of harm due to beryllium has not helped our relations either with our employees or with the rest of the community

* President, Clifton Products Company, Painesville, Ohio

Generally speaking, the workers in plants like that of my company can be divided into two groups. One group, comprising 90 per cent of the employees, consists of those who have served in the industry for many years. Because their employment started long before the installation of safeguards, these people have all been exposed to the dangers associated with the industry. Yet as a group they have never been subject to any serious pulmonary or skin trouble It has been among the second group, the remaining 10 per cent, that all the pulmonary and skin troubles have occurred.

Through the years we have become accustomed to visitations by representatives of all the government agencies concerned with the production of beryllium and with industrial health problems. Our attitude has always been completely cooperative; indeed, we have solicited the help of these agencies I am confident that management will continue in this attitude, and in this I feel that I speak for the entire industry.

Recently, we have been given some new and helpful tools, namely, well-planned pre-employment examinations, periodic tests for all employees, and promising therapeutic methods On the whole, however, we find ourselves still in about the same position that we were in seven years ago Though we have installed safety devices in the plants, we find that the tremendous range of susceptibility among the employees has minimized the effects of these safeguards It appears that from the standpoint of safety engineering, any job that falls short of perfection is of questionable value, but the engineering of a perfect job seems economically ruinous

The beryllium industry is indeed the patient. It is a young patient, hopeful of a brilliant future Its very life depends on the discoveries to be made by the members of this symposium and by similar groups.

I have prepared a few questions to put to the medical profession These questions, I believe, are typical of those in the minds of men responsible for the management of plants producing and using beryllium

1 Do you think that the dangers to health in the industry could be controlled or eliminated by protective apparatus in the plants?

2. Do you think that the hazards could be controlled or eliminated by periodic examinations of employees and by rigid control of their personal hygiene?

3. Would the combination of both of these measures lead to an elimination of the danger?

4 Assuming that no threshold, no maximum daily level of exposure consistent with safety can be definitely established, are you willing to suggest an empirical level?*

5 What measures do you think would constitute a complete periodic examination of all employees?

6 What beryllium salts or compounds do you consider most active in producing pneumonitis?

7 Do you think that beryllium oxide in its various degrees of calcination may produce pneumonitis, or is there some possibility that traces of beryllium salts remaining in the oxide as contaminants may produce the disease, depending on the individual degree of susceptibility?

8 Does metallic beryllium produce the disease?

9 Do you feel that a safe maximum daily level of exposure would be based upon the individual salt and would vary according to the activity of that salt or compound, or would this level be based purely on the element itself?

10. What program for personal hygiene would you recommend in plants where beryllium is handled?

11 Are you ready at this time to say that through the treatment of cases, some things have been learned which could possibly be of help in efforts to prevent the disease or to arrest it in the early stages?

12. How soon after pneumonitis has been recognized do you recommend the administration of penicillin or streptomycin?

13 Would you say that seasonal inoculation of employees against influenza and head colds would help?

14 Can you correlate in any way the occurrence of the disease with weather conditions and the prevalence of common infectious diseases?

15. Can you correlate the dermatitis with susceptibility to pneumonitis?

16 Do you recognize more than one form of the dermatitis and, if so, have you found that all forms respond to treatment with benadryl?

17 If there is a possibility of correlating the incidence of dermatitis with the incidence of pneumonitis, would it be too farfetched to think of treatment with benadryl to prevent pneumonitis?

* See references 173a and 174 (*Ed*)

Generally speaking, the workers in plants like that of my company can be divided into two groups. One group, comprising 90 per cent of the employees, consists of those who have served in the industry for many years. Because their employment started long before the installation of safeguards, these people have all been exposed to the dangers associated with the industry. Yet as a group they have never been subject to any serious pulmonary or skin trouble. It has been among the second group, the remaining 10 per cent, that all the pulmonary and skin troubles have occurred.

Through the years we have become accustomed to visitations by representatives of all the government agencies concerned with the production of beryllium and with industrial health problems. Our attitude has always been completely cooperative, indeed, we have solicited the help of these agencies. I am confident that management will continue in this attitude, and in this I feel that I speak for the entire industry.

Recently, we have been given some new and helpful tools, namely, well-planned pre-employment examinations, periodic tests for all employees, and promising therapeutic methods. On the whole, however, we find ourselves still in about the same position that we were in seven years ago. Though we have installed safety devices in the plants, we find that the tremendous range of susceptibility among the employees has minimized the effects of these safeguards. It appears that from the standpoint of safety engineering, any job that falls short of perfection is of questionable value, but the engineering of a perfect job seems economically ruinous.

The beryllium industry is indeed the patient. It is a young patient, hopeful of a brilliant future. Its very life depends on the discoveries to be made by the members of this symposium and by similar groups.

I have prepared a few questions to put to the medical profession. These questions, I believe, are typical of those in the minds of men responsible for the management of plants producing and using beryllium.

1. Do you think that the dangers to health in the industry could be controlled or eliminated by protective apparatus in the plants?

2. Do you think that the hazards could be controlled or eliminated by periodic examinations of employees and by rigid control of their personal hygiene?

3 Would the combination of both of these measures lead to an elimination of the danger?

4 Assuming that no threshold, no maximum daily level of exposure consistent with safety can be definitely established, are you willing to suggest an empirical level?*

5. What measures do you think would constitute a complete periodic examination of all employees?

6 What beryllium salts or compounds do you consider most active in producing pneumonitis?

7 Do you think that beryllium oxide in its various degrees of calcination may produce pneumonitis, or is there some possibility that traces of beryllium salts remaining in the oxide as contaminants may produce the disease, depending on the individual degree of susceptibility?

8. Does metallic beryllium produce the disease?

9 Do you feel that a safe maximum daily level of exposure would be based upon the individual salt and would vary according to the activity of that salt or compound, or would this level be based purely on the element itself?

10 What program for personal hygiene would you recommend in plants where beryllium is handled?

11. Are you ready at this time to say that through the treatment of cases, some things have been learned which could possibly be of help in efforts to prevent the disease or to arrest it in the early stages?

12. How soon after pneumonitis has been recognized do you recommend the administration of penicillin or streptomycin?

13. Would you say that seasonal inoculation of employees against influenza and head colds would help?

14. Can you correlate in any way the occurrence of the disease with weather conditions and the prevalence of common infectious diseases?

15. Can you correlate the dermatitis with susceptibility to pneumonitis?

16 Do you recognize more than one form of the dermatitis and, if so, have you found that all forms respond to treatment with benadryl?

17 If there is a possibility of correlating the incidence of dermatitis with the incidence of pneumonitis, would it be too farfetched to think of treatment with benadryl to prevent pneumonitis?

* See references 173a and 174 (*Ed*)

Further Discussion

MR. WINDECKER. Do you feel, Dr. DeNardi, that the danger could be controlled by protective apparatus in the plant?

DR. DENARDI Unquestionably, improvement of the engineering aspects of the chemical processes will help considerably toward eliminating the hazards we are confronted with in the plants.

MR. WINDECKER Do you feel that the danger could be controlled or eliminated by periodic examinations of the employees and by rigid control of their personal hygiene?

DR. DENARDI I have stressed the fact that medical vigilance is essential for some control of the various manifestations of the disease. Our present procedure consists of periodic examinations of all employees active in production, and immediate examinations of all persons who show evidence of infection or irritation of the upper respiratory tract.

We have instituted a prophylactic lay-off system Because infection or irritation of the upper respiratory tract is considered a predisposing factor in bronchitis or pneumonitis, a person with such a condition is not permitted to work until it has cleared up, although he receives a high percentage of his base pay

MR. WINDECKER: Do you think that either by better engineering or by medical vigilance, or by a combination of both, the danger can be eliminated?

DR. DENARDI. I do not believe that we can totally eliminate the factor that produces the disease I am of the opinion, however, that the dispersion of the offending particles in the atmosphere of a plant can be reduced to a minimum, so that only hypersensitive individuals will develop the disease

Devices for reducing the exposure of the workers, improved methods for the extraction of beryllium, and constant medical vigilance are essential if the hazards are to be controlled in the future

MR. WINDECKER Assuming that no threshold, or safe maximum of daily exposure, could be established as factual, would you be willing to suggest an empirical level?

DR. DENARDI As I have stated, host sensitivity must be considered an

important factor in causing the disease An empirical safe maximum may be determined by dust counts made at different times of the day Even in a supposedly safe atmosphere, however, although the "normal" person will not develop any of the symptoms of beryllium poisoning, the hypersensitive person in all probability will develop some form of the disease It will be difficult to eliminate completely this factor of individual susceptibility.

Nevertheless, minimizing the daily exposure undoubtedly will reduce the incidence of the disease

MR WINDECKER What beryllium salts or compounds do you consider most active in causing pneumonitis?

DR DENARDI. Beryllium fluoride is unquestionably one of the salts that is causing pneumonitis The fluoride process undoubtedly has been responsible for the largest number of cases not only of pneumonitis, but also of dermatitis Beryllium sulfate tetrahydrate has been considered another contributing factor in the insidious type of pneumonitis, whereas the anhydrous beryllium sulfate, in my opinion, is the probable cause of the fulminating type I understand that this compound is unstable and is the product of a violent thermochemical reaction, and I assume therefore that its concentration in the atmosphere, though it may be very brief, may be extremely intense

MR WINDECKER: There has been some suspicion of beryllium oxide Do you think that the oxide in itself, in any of its various degrees of calcination, may cause pneumonitis, or do you think there is some possibility that traces of beryllium salts remaining in the oxide may be responsible?

DR. DENARDI· In the two plants under my medical supervision I have not encountered any difficulty with pure beryllium oxide, and we have had workers who were employed continuously in that particular department for periods of several years Small amounts of the fluorides or sulfates, which are volatile to a certain degree, may cause bronchitis or pneumonitis. I believe that beryllium oxide is less likely to be pathogenic than those compounds are

MR WINDECKER. Do you have the same opinion in regard to metallic beryllium?

DR DENARDI Yes This form of beryllium may contain less than 0 5 per

Table IV diseases of the respiratory tract after exposure to beryllium

Authors	*Date of Publication*	*Character of Beryllium involved*	*Diagnosis*
Weber and Engelhardt [619] (Germany)	1933	Be metal (extraction)	Bronchiolitis
Fabroni [186] (Italy)	1935	Be CO_3	"Beryllıosis" (animals) Forms of pneumonia
Gelman [227] (Russia)	1936	Be metal Be oxyfluoride	"Metal fume fever" Broncho-alveolitis
Berkovits and Izrael [67] (Russia)	1940	Be metal Be fluoride Be oxyfluoride	Fluorine-beryllium vapor intoxication Acute bronchiolitis Pulmonary sclerosis
Meyer [412] (Germany)	1942	Be silicate Be hydroxide Be sulfate Be chloride	Beryllıosis Chronic large-celled pneumonia

VanOrdstrand and others[675] (Ohio)	1943	Beryl ore Be oxide	Chemical pneumonia
Shilen and others[657] (Pa.)	1944	Be ore Be fluoride Be oxide	Respiratory ailments Dermatitis
Kress and Crispell[344] (Pa.)	1944	Fluorescent powder Be carbonate Be manganese silicate	Atypical pneumonitis
VanOrdstrand and others[676] (Ohio)	1945	Be metal Be oxide Be sulfate Be fluoride Be oxyfluoride	Beryllium poisoning Contact dermatitis Contact conjunctivitis Chemical nasopharyngitis Chemical pneumonitis
Hardy and Tabershaw[284] (Mass.)	1946	Fluorescent powder Zinc manganese beryllium silicate	Delayed chemical pneumonitis

animals in support of the theory that some compounds of beryllium are pathogenic for man.[109, 131, 182, 183, 185, 411, 675] Diagnoses of pulmonary sclerosis and chronic large-celled pneumonia made in cases in Massachusetts seem to corroborate the existence of a second clinical type of pulmonary disease in the beryllium industry abroad.

The epidemiology in America also is outlined in table IV. One notes that in the United States as in Europe, a wide variety of beryllium compounds appeared in the industrial environment of the patients, and that the several diagnoses fall into two clinical categories, chronic and acute Both types of disease affected primarily the respiratory tract, and to the attending physicians both suggested chemical pneumonia Unpublished reports received by the Division from physicians mention single cases and groups of cases, in both the chronic and acute categories, arising in Connecticut, California, and New Jersey, as well as in Ohio, Massachusetts, and Pennsylvania, in industries using beryllium in some form Thanks to Dr Willard Machle and Mr E. W. Thompson, we have sound clinical and pathologic evidence of the basically important fact that a beryllium worker who has had more than one attack of the acute disease of the respiratory tract may develop chronic disease. These reports seem to be strong evidence that in the beryllium industry toxic materials are used which are capable of causing disease of the respiratory tract in man

The following material shows the character of the illness occurring among Massachusetts workers engaged in the fluorescent lamp industry. These workers were exposed to zinc manganese beryllium silicate Because composition of the phosphor varied during the years in which these cases were developing, we have no knowledge of the intensity of the exposure of any given patient No one operation in fluorescent lamp manufacture can be shown to have resulted in a greater number of cases than did other operations No habit of work, such as the famous brush sucking of the painters of radium dials, has been discovered to be a common factor in causing what we have chosen to call "delayed chemical pneumonitis" This term, suggested by Dr. Joseph Aub, has proved very useful, especially when lengthened to "delayed chronic chemical pneumonitis."

Because more cases are currently being discovered, no figure on the incidence of the disease would be reliable At present we have in our

files records of 45 cases in Massachusetts (see table V) These 45 patients, of whom 13 were men and 32 were women, were employed in fluorescent lamp factories for periods ranging from four months to eight years. The most startling single fact about this series is that out of 39 cases which were adequately studied, in 27 the onset of symptoms followed exposure after a delay ranging from one month to five years, hence the validity of the term "delayed chemical pneumonitis"

TABLE V OCCURRENCE OF CASES IN MASSACHUSETTS FLUORESCENT LAMP WORKERS

Year	*No of Cases*
1941	2
1942	2
1943	10
1944	3
1945	7
1946	12
1947 (to September)	9
Total	45

A second unusual fact which enters the picture is the appearance of additional cases which we call "neighbor cases" 3 instances in which persons living near a fluorescent lamp factory contracted an illness identical with that found among the industry's employees Of these 3 patients, 2 have died, and autopsies revealed the same pathologic effects as in the worker group. In a fourth case, in which the clinical picture is similar to that in the worker group, the patient is the mother of a worker who died of delayed chemical pneumonitis The late Dr Gardner told us of a single neighbor case of what appeared to be delayed chemical pneumonitis in Ohio Gelman[247] reported that in Russia watchmen stationed 150 meters from any operation in which beryllium was used developed pulmonary disease similar to that suffered by workers engaged in such operations With our present knowledge it is impossible to interpret these findings, but it is certain that they have grave implications for public health

With study of the Massachusetts cases during the past five years, it has become possible to define a unique clinical syndrome (see table

VI). The development of the disease was gradual in most cases The patients sought medical advice in most instances because of fatigue and loss of weight, followed by gradually increasing dyspnea on exertion,

TABLE VI SYMPTOMS AT ONSET

	No of Cases
Weight loss	38
Dyspnea	35
Anorexia	36
Cough	27
Weakness and fatigue	25

with or without cough. Anorexia and nervousness were prominent at the onset, especially among the women Frequently, mild coryza appeared and persisted When these symptoms failed to disappear, the patients

TABLE VII SYNDROMES AT ONSET

	No of Cases
Persistent respiratory infection with weight loss	12
Graves' disease	2
Rheumatoid arthritis	3

sought help. Some of the initial syndromes are listed in table VII, of special interest are the 2 cases in which the disease simulated Graves' disease and 3 in which it simulated rheumatoid arthritis. The possibility

TABLE VIII PREDISPOSING FACTORS

	No of Cases
Pregnancy during "delay"	11
Chronic respiratory infections	7
Fatigue (in soldiers)	4
Allergy	2

was recognized that respiratory infections, pregnancy, and unusual fatigue might have been factors in precipitating the onset of the disease in some cases (see table VIII).

At the onset of symptoms the clinical picture and the roentgenologic

pattern, which is described by Dr. Wilson,* were similar in all cases. The development of the disease varied, however. A cough, with or without sputum, occurred in some cases. Extremely shallow breathing and dyspnea increasing to orthopnea were striking in at least 5 of the 15 cases which I have had the opportunity to follow up. In some cases the anorexia persisted, but in others it disappeared completely at an early stage. Nausea and vomiting, especially when concomitant with coughing bouts, were often hard to handle.

TABLE IX. PHYSICAL FINDINGS

	No. of Cases
Abnormal auscultatory signs	24
Cyanosis	10
Cardiac changes	8
Clubbing of fingers	5
Lymphadenopathy	5
Enlargement of liver	4
Skin lesions	3
Enlargement of spleen	3
Enlargement of thyroid gland	2

The positive findings on physical examination (table IX) were not striking. Because of the loss of weight and the dyspnea, which were serious in most instances, the patients developed a characteristic miserable appearance. Except in terminal episodes the temperature was only slightly elevated, but the pulse rate was generally increased. Inconstant auscultatory signs were the rule. Clubbed fingers were reported in 5 cases, and definite cyanosis was noted in 10. The liver was enlarged in 4 cases, and the spleen in 3. Lymphadenopathy was found in 5 cases and enlargement of the thyroid gland in 2. Eight patients who were seriously ill developed right-sided enlargement of the heart. Single and multiple skin lesions, nodular in type and transitory in occurrence, were recorded in 3 cases. No bone lesions were recorded.

The laboratory studies in this interesting series of cases are by no means complete. We can report, however, that smears and cultures of sputum were all negative for the tubercle bacillus (table X). Tests of blood and sputa for other pathogenic organisms gave negative results.

* See Chapter 9. (Ed.)

TABLE X. TESTS FOR TUBERCLE BACILLI

	No. of Cases
Sputum examinations	
Negative for tubercle bacilli	22
Negative for yeast and fungi	3
Tuberculin tests	
Negative	13
Positive	2
Cultures for tubercle bacilli	
Negative sputa	16
Negative gastric washings	2

In rare instances, skin tests for an acid fast organism showed a positive reaction. Secondary polycythemia has developed in 3 cases, but otherwise the blood elements show no change (table XI). Sedimentation

TABLE XI BLOOD COUNTS AND SEDIMENTATION RATES

	No of Cases
Blood counts	
R B C more than 5,000,000	3
W B C 9,000-11,000	4
W B C 4,000-6,000	5
Marked disturbance in differential	2
Sedimentation rates	
Slightly elevated	6
Normal	8

rates show little change (table XI) Abnormally high amounts of globulin, calcium, alkaline phosphatase, and total serum protein were found in the blood of a few of the patients who were most seriously ill (table XII) In one case the increase in blood calcium was correlated with the

TABLE XII. BLOOD CHEMISTRY

	No of Cases	Findings	Range	Average
N P N over 30 mg	3			43 mg
Total protein	6		6 3 —7.8	7 0
Albumin	4	2 7, 4 2 4 48, 3 98	2 7 —4 48	3 84
Globulin	4	3.9, 3 41, 2 94, 3 3	2 94—3 9	3 39
Calcium	1	11.7 mg		
Phosphatase	1	6.7 units		

passage of a kidney stone. Vital capacity studies as done in hospitals are only approximate indexes of pulmonary function As one might expect, however, in all these cases of delayed chemical pneumonitis, whenever an effort was made to test the vital capacity it was found to be diminished.

A punch biopsy of the liver of one moderately ill patient was made at the Massachusetts General Hospital This examination was made in spite of normal results in liver function tests, because the anorexia and loss of weight suggested liver involvement Dr Tracey Mallory reported tubercle-like collections of cells of epithelioid character between normal strands of hepatic structure We are hoping that it may prove safe to do liver biopsies in other cases Biopsies of skin lesions and lymph nodes have been variously reported as revealing true Boeck's sarcoid, chronic granulomatous inflammation, and tubercle-like lesions without caseation.

Oxygen has been useful in the treatment of the acutely ill patients in this series A few patients report that prompt use of an oxygen mask aborts a spell of coughing, and that they observe a change in the color of the lips and fingernail beds One patient's husband, a good observer, reports that his wife's respiration rate drops from 60 to 30 breaths a minute after a few minutes of inhaling oxygen My colleagues and I at the Division wonder if more regular use of oxygen would not be physiologically sound Patients well enough to travel believe they have been benefited, probably through freedom from respiratory infections, by trips to Florida and Arizona The sulfonamide compounds, penicillin, and cytochrome-C have been tried in cases of delayed chemical pneumonitis, without success. At Dr Gardner's suggestion BAL, or British Anti-Lewisite, was tried by the Harvard Department of Pharmacology on dogs poisoned by beryllium, with no evidence of benefit Arsenicals have been administered, with reported partial success to one patient whom we have not seen. Because of the loss of weight in these cases and because of the findings in the one liver biopsy, concentrated feeding is now being tried.

Keeping the patients' morale high has been a real problem, partly because of the ceaseless dyspnea, and partly because the patients know of the deaths among their fellow workers and are keenly aware of the mystery surrounding the etiology of this disease.

On the basis of our experience with these 45 cases, we have arbitrarily

divided them into several categories according to the severity of the disease (table XIII). The severe cases for the most part were those which appeared earliest in this series; the complications occurred in this group Loss of as much as 40 pounds in weight in the first year of illness, and dyspnea and orthopnea producing respiratory rates as high as 60 breaths a minute, were characteristic symptoms Profound anorexia, with nausea and vomiting at times, occurred in the clinical course of the disease. In this "severe" group, 7 of the 15 patients died after periods of illness varying from eight months to four years One patient in this group has become completely well clinically after an illness lasting nearly three years.

TABLE XIII CLINICAL TYPES OF DELAYED CHEMICAL PNEUMONITIS

	No of Cases
Severe	15*
Moderately severe	18
Mild	8
Asymptomatic	4
Total	45

* Of these cases 7 ended fatally

We have classified as moderately severe 18 cases in which the characteristic effects are the loss of as much as 25 pounds in weight in the course of the disease, and dyspnea with an average respiratory rate as high as 30 breaths a minute Anorexia in the early stages of the illness, and vomiting following the bouts of coughing, are regularly reported

In 8 cases classed as mild the patients have lost less than 10 pounds in weight, cough little or not at all, have no gastrointestinal symptoms, and experience dyspnea only on exertion. The chest roentgenograms and occupational histories, however, make it correct to include these cases in the series

Routine chest roentgenograms of 4 workers who were exposed to beryllium compounds at the same time as workers who became clinically ill showed the pulmonary changes characteristic of the disease, but so far these 4 people have developed no symptoms

In some cases the duration, course, and outcome of this disease were

affected adversely for the patient by the complications listed in table XIV All patients reported that the slightest respiratory infection increased the dyspnea and also the coughing, if a cough was one of the symptoms, and the amount of sputum

TABLE XIV COMPLICATIONS OCCURRING DURING THE DISEASE

	No of Cases
Congestive heart failure	8
Acute respiratory infections	7
Pregnancy (after onset)	4
Kidney stones or colic	4
Spontaneous pneumothorax	3
Emergency surgery	2

In five years the prognosis in these cases has changed markedly Although six deaths occurred among the first 17 patients, as yet only seven deaths have occurred among 45 patients (see table XV), the mortality rate therefore is 16 per cent Of the 45 patients, 27 are still functionally disabled, 14 completely and 13 partially, after an average illness of two years. Seven patients in a sense are convalescent, they are

TABLE XV CONDITION OF PATIENTS IN SEPTEMBER, 1947

Dead	7
Disabled	
Completely	14
Partially	13
Convalescent (working)	7
Asymptomatic	4
Total	45

well enough to work. These 7 have been ill for an average period of 18 months. Four patients, as I have previously mentioned, are free from symptoms Of the 7 patients who died, the majority were ill for approximately two years, one died after four years of illness Among the disabled patients the period of illness varies from four months to a little more than two years Delayed chemical pneumonitis is shown by this data to be usually a severe illness of long duration

In each case differential diagnosis requires consideration of infection by acid-fast organisms, of Boeck's sarcoid, and of silicosis. So far no tubercle bacilli have been discovered in sputa or in cultures of postmortem material, but secondary infection by acid-fast organisms may be a possible complication of this disease.

In our study of the literature and in discussion with clinicians and pathologists, my colleagues and I have developed a definite point of view on Boeck's sarcoid. To the pathologist Boeck's sarcoid presents a unique histologic picture, reasonably well defined, of unknown etiology. Perhaps, as French research workers postulate,[327, 463, 464] the disease is the response of certain conditioned tissue to a variety of stimuli. The clinician sees Boeck's sarcoid as a relatively benign granulomatous disease characterized by transient skin lesions, by bone changes visible on x-ray examination, by transient pulmonary x-ray findings, by enlargement of the lymph nodes and spleen, by increase in serum globulin, and in rare cases by a bizarre involvement of the eye, parotid gland, and tonsil. Delayed chemical pneumonitis on the other hand, as yet has produced no bone lesions, it is a severe disease with a poor prognosis, only occasionally has it been accompanied by an increase in serum globulin. Patients with delayed chemical pneumonitis have a common factor in their occupational backgrounds. Furthermore, pathologists do not agree that autopsies in cases of delayed chemical pneumonitis revealed the characteristic lesions of Boeck's sarcoid.

An atypical form of silicosis seems to be ruled out by several facts: delayed chemical pneumonitis is more severe in the early stages than is silicosis, the silicotic nodule is not seen in postmortem studies of the lungs, silica is not recovered in any appreciable quantity from the lung ash of victims of delayed chemical pneumonitis. Even more crucial as a differential point is the epidemiologic evidence that delayed chronic chemical pneumonitis has developed in workers in the beryllium industry who have never been exposed to a beryllium compound containing silica.

I have attempted to outline the epidemiology and to point out the chief clinical features of an occupational illness which apparently was discovered only recently, and which my colleagues and I have designated as delayed chemical pneumonitis. Lacking a satisfactory quantitative test for beryllium in the air, chemists and engineers in the field of indus-

trial hygiene have been unable to help toward settling definitely the question of the etiologic relationship of beryllium compounds to this disease. The incrimination of beryllium is based on its presence as the common denominator in the working environment of patients suffering with various types of pulmonary disability.

Conclusions

1 The distinctive clinical features of this disease are an unusual delay in the onset of symptoms, striking dyspnea and loss of weight, and the long duration of the illness There is always a history of exposure to beryllium compounds, generally in the past

2 A differential diagnosis ruling out pulmonary tuberculosis, silicosis, and Boeck's sarcoid as definitely as possible is necessary in each case

3 Although the etiology of delayed chemical pneumonitis is not yet clearly established, clinical and experimental evidence is accumulating which incriminates beryllium compounds.

4 There is evidence that cases of delayed chemical pneumonitis as well as of acute chemical pneumonitis are appearing in various parts of the United States, where workers are exposed to beryllium compounds.

Discussion

THOMAS L SHIPMAN, M.D *

Dr Hardy is a comparative newcomer to this investigation, she has been in it only for a couple of years She has made up for lost time, however While some of the experts were following will-o'-the-wisp clues, she undertook the rather thankless but necessary chore of finding out as much as she could about the patients With utter disregard for both shoe leather and automobile tires, she followed them up, did everything but move into their houses and live with them. Her factual account represents many hours of talking not only with patients but also with their relatives, friends, and family physicians, to say nothing of plant managers, foremen, engineers, industrial hygienists, and plant physicians. Her tireless search has been for factors common to all cases So far it

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appears that the one common denominator is the presence, in the past environment, of beryllium

I should like to emphasize and enlarge upon a few points which Dr Hardy made. First, I should like to point out how easy it is to diagnose the fully developed disease, in spite of the small number of diagnostic criteria. Overwhelming dyspnea, plus a chest roentgenogram which is nearly unmistakable, plus a history of exposure to beryllium, gives the diagnosis. So far no tests have been developed which will confirm or disprove the diagnosis. Make no mistake, however, there are plenty of baffling diagnostic problems in some of the borderline cases.

I wish, too, to emphasize the vividly dramatic picture presented by the fully developed disease. Picture for yourself a young man just out of college, one who had been on the track team, reduced to the point where shortness of breath would not permit him to walk more than a few steps at a time Picture an attractive girl in her early twenties down from the normal 125 or 130 pounds to 85 pounds, and with a respiratory rate of 40 to 50 at rest!

The onset of symptoms often may be gradual, but also may be dramatically sudden. One girl whose roentgenogram showed the characteristic pulmonary changes stated at the time, in response to direct questions, that she felt perfectly healthy, with no cough or shortness of breath Yet within three or four weeks she was gasping and cyanotic, and was hospitalized. This occurred nearly two years after she had left the fluorescent lamp factory.

The astonishingly long latent period, and the appearance of pulmonary changes before the onset of symptoms, are extremely interesting. One young man, now a patient at Trudeau, had negative chest roentgenograms for four years after his exposure ended Yet after another 14 months his roentgenogram showed the characteristic abnormalities, and some weeks later he gradually developed orthopnea.

The disease process, as you will hear from the pathologists, is not confined to the lungs It is hard to say whether we are dealing with a pulmonary disease with extensions to other parts of the body, or with a systemic disease producing predominantly pulmonary lesions The cases do seem to fall into certain groups, each with symptoms which seem to be a variation on a central theme Although the number of cases is small, some patients have exhibited sarcoid-like skin lesions, others have re-

sembled patients with Graves' disease, still others have developed arthralgia, and in some patients the presence of gallstones and renal calculi has suggested metabolic disease

Do not lose sight of this point whereas the Massachusetts patients supposedly were exposed to zinc beryllium silicate and perhaps some amorphous silica, it seems probable that a smaller group in Connecticut developed the same disease after exposure presumably to beryllium oxide without benefit of silica or a silicate Many people believed that in the acute cases in Ohio and Pennsylvania the disease was a reaction to the sulfate or the fluoride of beryllium, it is probable, however, that some young research engineers in a Massachusetts university acquired the same condition through exposure to beryllium oxide only I cannot state with complete conviction that beryllium oxide was the sole offender in these instances Here, though, are some of the apparently incompatible findings which have plagued investigators We hope that this symposium will clarify the matter for all of us

We still have no answer to the question with the large numbers of people working in the same industrial environment, why was such a comparatively small group affected? Dr Gardner postulated the theory that the disease is due to exposure to the fluorescent powders, plus some other factor which was still a mystery to him I certainly have no key to this puzzle, but I feel that whoever can provide it will be well on the way toward the solution of the entire problem

Further Discussion

DR SHIPMAN: Previous discussions failed to enlighten me on one point. It has been stated that the percentage of beryllium in the phosphors used in the Salem plant was changed sometime in 1942 I am under the impression that all or nearly all of the patients in the series of cases which Dr Hardy has discussed suffered their exposure during the era of the early formula I seek enlightenment, feeling that this point possibly may help to explain why so far—I want to emphasize that phrase "so far"—the incidence of the disease has been far greater in one plant than in other plants

MR. MORSE Our original formula for zinc beryllium silicate called for about 12 per cent beryllium oxide In 1942 we greatly reduced that per-

centage. At about the same time, war requirements led to restrictions on the use of beryllium, and so the proportion of beryllium oxide was brought down to about 2 per cent, which was more nearly in line with the percentage used by other manufacturers That fact may explain why all our cases appear to result from exposure in the period before 1943

MR. MERRILL: It might be well to clarify the question of those percentages a little There are two main forms of lamps: the daylight lamp and the white lamp The white lamp contains about 90 per cent zinc beryllium silicate and 10 per cent magnesium tungstate, whereas the daylight lamp contains about 50-50 silicate and tungstate.

After discussing the subject with Dr Nichol, I wish to make this distinction between the two types clear. In the white lamp, although the proportion of beryllium oxide in the silicate itself may have run as high as 14 or 15 per cent, dilution of the silicate with magnesium tungstate would have reduced the proportion in the final powder to about 12 per cent In the daylight powder when the silicate had been blended with the tungstate the proportion of beryllium oxide would have run about 6 or 7 per cent

I should like to discuss in a little more detail the case which Dr Shipman mentioned, that is, the one in which the patient had both the acute and the chronic disease. That individual was exposed, not to beryllium fluoride or beryllium sulfate or any of the more active chemicals, but to beryllium oxide and zinc beryllium silicate, and he had both an acute form and the chronic form of the disease.

MR. MORSE. Am I correct in stating that the change in formula cut the proportion of beryllium oxide to 4 per cent?

MR MERRILL. It has run between 2 and 2 5 per cent in the white lamps since early 1942 The preliminary conversion was started in February 1942, and the new powder was gradually put into production, starting in May 1942

MR. MORSE You indicate that a high percentage of beryllium and a low percentage gave the same efficiency. Is that because the formula is a complicated one, so that a balancing of different elements, rather than the amount of beryllium, determines the result?

MR. MERRILL. I'm not prepared to discuss that question in detail, because a lot of engineering is involved in the whole problem, many

changes were made along other lines at the same time that the change was made in the formula. I should say that the old and the new formulas gave essentially the same efficiency.

MR EISENBUD I should like to get definite information, did all these patients work in the plant before 1942?

DR SHIPMAN. I think this discussion has raised a very important point We have records of patients who developed the disease after exposure only to the powders with a low beryllium content I should like to ask Dr Hardy about that

DR HARDY: Of the 45 patients in the series, 43 worked in the one plant that has had so much trouble. Two worked in another plant which I believe used General Electric powders, and if I understood the information we have received on that point, those 2 people were never exposed to powders with a beryllium content higher than 4 per cent

In the group of 43 there were 2 or 3 young women who were too young to have been working in the earlier days

MR MORSE. In answer to the specific question, "Has Sylvania had cases of the disease among employees who could not possibly have been exposed to the high percentage powder?" we think not The dates of exposure in some cases of illness, however, are beginning to crowd toward the date when we made the change in formula, and this fact is causing us real anxiety.

It should be pointed out that the dates which Mr Merrill gave for the change apply to the production of the zinc beryllium silicate powder Like all manufacturers we have a backlog of inventory, and our dates for discontinuing the use of the high percentage powders in manufacturing lamps would lag behind his production dates by some months. Dr Williams, who made a survey of our operations, reported that in August and September of 1944 we had two batches of the high percentage powder These were the last batches that we put into lamps That is why there is some hesitation about the exact answer to Dr Shipman's question No one knows what the next case may show

We believe, nevertheless, that every case discovered so far among Sylvania employees can be accounted for in terms of exposure to the high percentage powder

DR. HERMAN. I'd like to ask Dr. Hardy what pulmonary changes the roentgenograms showed in the patient who was convalescing after a period of illness of. I think, 18 months?

DR. HARDY: Even in this young man who is well, who has no symptoms whatever and has gone back to work, there is a residual effect which under other circumstances, I think, roentgenologists would call pulmonary fibrosis.

DR HERMAN I'd like to know the general range of the latent period.

DR HARDY: The first few patients to become acutely ill became ill on the job They were older people who had been with the firm a number of years and were there when the company began to make fluorescent lamps. These were the first 3 or 4 cases in the series.

In 27 of the 39 cases which were adequately studied, the onset of the disease was delayed. The latent period varied widely, from one month to five years.

DR SMITH I believe that Dr. Hardy knows of 2 cases of delayed or chronic pneumonitis occurring in workers handling fluorescent powders containing 4 per cent beryllium oxide I'd like to know in detail what these people were doing

DR HARDY. Of the two plants manufacturing fluorescent lamps in Massachusetts, one had no report of illness until March 1947, when the first case traceable to that factory appeared in one of our local hospitals This young woman had been engaged in fluorescent lamp manufacturing, doing as apparently all such workers did in the years around 1941, that is, going from one station in the plant to another. She had worked in the so-called stem department, and in the exhaust department, and then had left She had gone with her husband to various army camps, and then had become a clerk in an office. Her illness was diagnosed originally, in New Hampshire, as tuberculosis, and she was sent to Boston for study She is going down hill rapidly

The other patient, with whose case I am not as familiar as I should like to be, worked along with the first young woman She has a cough and shortness of breath, and has been in several local hospitals recently.

DR WILLIAMS During the early stages of the development of fluorescent lamps the manufacturers were using tubing of lead glass, and when one of the longer 40-watt tubes proved defective at one end, they would cut

off the end and salvage the tube by making it into a smaller one. This is the process in which this girl was engaged (Incidentally, she worked in the plant for a total of 520 hours) Her job consisted entirely of cutting off these tubes by thermal shock, after heating a tube, she brought a rapidly revolving steel wheel against it, and it snapped from the shock Dust resulted from this operation

MR. URBAN. Earlier in this discussion, mention was made of a person who apparently suffered from the acute form of the disease at two different times before he became ill the third time, then of the delayed or chronic form Was exposure to beryllium in this instance related to fluorescent powders?

MR MERRILL The man had the acute form once and the delayed form once, he did not have the acute form twice

MR URBAN Did this individual's beryllium exposure result from fluorescent powders?

DR HARDY Apropos of the case just mentioned the early records made by Crispell[144] in Pennsylvania in 1943 and 1944 were those of men who were making fluorescent powders.

Besides the patient of whom Mr Merrill speaks, there was a man employed in the manufacture of beryllium alloys who had acute chemical pneumonitis twice After the second attack he did not go back into the beryllium-containing atmosphere, but nevertheless he suffered a relapse and died

At autopsy the lesions in this case could not be distinguished from those found at autopsy in cases in the fluorescent lamp series That fact is important from the epidemiologic standpoint, we have a very definite hook-up between the two types of pneumonitis

I want to say in closing that I don't think we should be disturbed at this time about the incidence of delayed chemical pneumonitis When I went to San Francisco in June to tell the National Tuberculosis Association about this, there were 36 cases, this is September, and there are now 45 cases

This disease is a new clinical entity, and it appears in an industry using materials which we don't know much about as yet. My laboratory friends tell me that beryllium baffles them I think that as a group we should accept the fact of this new disease in industry

CHAPTER 9

Roentgenologic Aspects

S. A. WILSON, M.D.*

I have been asked to discuss the roentgenologic aspects of chronic pulmonary granulomatosis probably caused by beryllium and its compounds I think it is safe to assume that this request was made not because of any special talent of mine for roentgenologic differential diagnosis, but because I have had opportunities to examine many of the Massachusetts fluorescent lamp workers who developed the disease, and to study the chest films made in a number of other cases. Our Massachusetts series consists of more than 40 cases, and the collection of roentgenograms in this series has been augmented with borrowed films, some of patients with histories of employment in the fluorescent lamp industry, and some of employees of other industries, including the extraction of beryllium from the ore Chest roentgenograms of workers in brass foundries and of people employed in the manufacture of neon signs or of abrasives have been made available to me for study and comparison.

In the study of any disease it is desirable to divide its development into stages, if possible Dr. M C. Sosman of Boston and I attempted to do this for the article prepared by Dr. Hardy and Dr Tabershaw[264] in 1946 We reviewed the roentgenograms of 12 of the 17 patients discussed in the article These roentgenograms gave us the impression that the disease progresses through three recognizable stages, not including the latent period During the latent period, which varies from three months to three years, the lungs appear normal in a number of cases The earliest recognizable roentgenologic variation from the normal, in what we called stage 1, was a fine, diffuse granularity resembling fine sand We observed no increased linear markings, no nodulation, no

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coalescence of the lesions, no pleural thickening or effusion The appearance of the lungs was not the even, relatively smooth ground glass effect seen in pulmonary edema or congestion, for the lesions, though uniform and diffuse, were distinctly particulate The affected area extended to the periphery and included both the apexes and bases, though at first



Fig 45 Second stage of pulmonary granulomatosis seen in a beryllium worker

glance the apexes and bases seemed to be spared (The late Dr Leroy Gardner in his description of the roentgenologic picture mentioned the same observation) The hilar vascular shadows seemed normal

In stage 2 there seemed to be a diffuse reticular pattern on the granular background (fig 45) The hilar vascular shadows had become fuzzy

and indistinct, and showed slight enlargement In only 3 cases could we be certain that the hilar nodes were enlarged.

In stage 3 distinct nodules, varying from 1 to 5 mm in diameter, were found uniformly distributed through the lungs In this stage the roent-



Fig 46 Third stage of pulmonary granulomatosis seen in a beryllium worker

genograms (fig 46) of several patients showed numerous small areas of diminished density among the reticulo-nodular shadows. In single films the appearance was that of the cut surface of a sponge We attributed these small intervening areas to the presence of emphysema The nodules were evenly distributed They did not coalesce, and showed no signs of calcification or cavitation. There was no definite evidence of linear

fibrosis The hilar shadows were still fuzzy and indistinct. The pleurae did not seem to be involved We saw no definite signs of emphysema at the bases, though in one case some upward displacement of the hila and the interlobar fissure on the right was noted The pulmonary artery was



FIG 47 Third stage of the disease, also showing evidences of cor pulmonale, in a beryllium worker

prominent in some cases, several of which showed the characteristic features of cor pulmonale (fig 47)

By now, having seen chest films from a larger number of cases, Dr Sosman and I have somewhat altered our conception of the roentgenologic changes and their classification It still seems desirable and necessary, however, to formulate some classification, if we can, in order to catalogue films and study cases Making a reliable classification has

proved extremely difficult for many reasons, including the fact that during the latent period the patients are free of symptoms, that the degree of disability varies, that in most cases we have been unable to obtain films of comparable quality, and that in many cases we have not had complete series of films because the patients were examined in various hospitals, in some cases in various localities.

Obviously, it is necessary to detect even earlier changes, if possible, than those we have been able to recognize so far In many cases at least, the pulmonary changes are progressive, and are irreversible in the stages now recognizable. Basing a theory on information received on a few cases of the acute form of the disease (one of which terminated fatally), we are now considering the possibility that patients developing the chronic type of disease may during the time of exposure have passed through a stage of congestion, with or without edema, such as is observed in the acute disease, but with so little disability that the condition is regarded by the patients or even by their physicians as of no significance.

Increased linear markings have been suggested as possibly the earliest roentgenologic signs of the disease. Such markings, however, are a questionable basis for an early diagnosis or even for suspicion of the disease, for opinion varies widely on what constitutes a change from normal to pathologic prominence. If earlier roentgenograms of the same patient are available, the linear markings may have diagnostic value and be accepted as representing stage 1 The fine, diffuse granular pattern will then indicate not stage 1 but stage 2 The diffuse reticular pattern on a granular background will indicate stage 3, and distinct, discrete nodulation, stage 4 We might add a fifth stage to our classification for cases in which cor pulmonale is observed, even though the general roentgenologic pattern does not change appreciably.

Throughout the later stages, although nodulation is the dominant roentgenologic feature, the granular "sand storm" background seems to persist Emphysema probably always occurs, at least in small areas, though it is less evident in some cases than in others. Upward displacement of the short interlobar fissure on the right, which Dr Sosman and I observed in 1946 in a single case and which I have since seen in several cases, probably indicates some emphysema in the lung bases.

The roentgenologic pattern seems sufficiently similar in all cases to be garded as possibly diagnostic The pattern seen in cases associated

with the fluorescent lamp industry is repeated in the roentgenograms of employees of other industries, but with some variations, which probably can be explained on the basis of differences in the degree of exposure or in the types of beryllium compounds used in the different industries

Many slight variations can be explained on the basis of technical failures The technical aspects of roentgenography must always be considered when films are compared for fine detail, as is necessary with this disease. Unfortunately, the films I have studied were made with a wide variety of equipment. Some were made with portable equipment in which the current was limited to about 30 milliamperes In some instances, the milliamperage was higher but still limited by a stationary target in the x-ray tube, a rotating target permits not only the use of more power but also a shorter exposure and a smaller focal area In other instances, plateholders with improperly fitting screens were used, and in still others the patients had not been accurately positioned Any of these factors can impair the quality of the roentgenogram and cause slight variations from the true picture.

The most significant feature of the characteristic picture is the uniform distribution of the fine granulation. The size of the nodules varies among cases, but their failure to coalesce, and the absence of evidence of calcification, cavitation, pleural reaction, tuberculosis, or other secondary infections seem significant

Beginning in 1942, roentgenologic surveys were made of nearly all employees in the fluorescent lamp factories in my vicinity. Surprisingly, although several thousand chest films have been made, only 2 cases of the disease have been discovered by this means Other cases have appeared, however, in persons whose first chest films were considered normal After recognizable roentgenologic changes appeared, a group of several roentgenologists studied the early films in these cases, but were unable to detect any significant variation from the normal

It is my opinion that the intervals between periodic examinations were too long, and that if we had been able to make mass surveys more frequently, we might have been able to discover these cases sooner. More frequent examinations, however, would have entailed an immense amount of work The use of photofluorography was considered, but the idea was discarded on the grounds that the slight pulmonary changes in the early stages of the disease probably would not be revealed by this method.

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Most of the patients gave histories of precipitating factors such as pregnancy or respiratory infection. Nearly all showed a decrease in vital capacity when the disease was well established. It may be that vital capacity is reduced in the latent period without the patient's becoming aware of any change, until the action of a precipitating factor produces severe symptoms Obviously, in the study of this disease the latent period must not be neglected

The extent of the pulmonary involvement varies somewhat in different cases In some roentgenograms the granulation is more prominent or the nodular shadows are smaller and closer together than in other cases Uniform distribution throughout both lungs is constant, however. The degree of disability in relation to the roentgenologic picture varies.

In roentgenologic differential diagnosis of diseases of the chest several points should be considered.

1 The density and contours of the shadows. In this connection one must keep in mind the fact that a roentgenogram is merely a shadow picture. Obviously, diseases which produce similar reactions in the lungs will cause similar shadows in the roentgenogram.

2. The location or distribution of the shadows. This point often is the key to differential diagnosis In some diseases the shadows characteristically appear in the bases of the lungs, whereas in other diseases they are seen in the apexes, in still others, in the middle of the lung fields. In some they appear in one or more lobes, and in certain diseases are distributed throughout the lung fields

3 The presence or absence of pleural involvement.

4. Possible enlargement of the lymph nodes

5 Possible increases in the prominence of the vascular markings.

6. Possible changes in the bony thorax.

7. Possible changes in the size, shape, or position of the mediastinal contents and diaphragm

Roentgenologic diagnosis is like clinical diagnosis in that the method often is inadequate. Although X-ra studies often a sound basis for diagnosis, different disea e closely ntgenograms in many cases. In such case genologis e use of all available clinical and labora d even find diagnosis impossib

To discrim pu omat cl

pneumonitis, from certain other diseases of the lungs may be extremely difficult without serial roentgenograms, a complete history including the occupational history, and clinical and laboratory data The clinical and laboratory data usually serve to eliminate the following acute diseases from consideration, but serial films often are necessary

Poisoning Through Inhalation of Toxic Gases To distinguish such conditions roentgenologically from the acute form of chemical pneumonitis is almost impossible, for the pulmonary changes produced are closely similar and the X-ray pattern therefore is essentially the same It is not difficult, however, to distinguish gas poisoning, which is characterized by pulmonary edema and consolidation, from the chronic form of chemical pneumonitis, with its particulate lesions.

Heart Failure In this condition the distribution of the shadows is significant They are seen mostly around the hila and in the bases of the lungs, with broad, soft linear markings radiating from the enlarged hila The heart shadow may be enlarged and may have an abnormal contour There is likely to be evidence of pleural effusion.

Nephritis As in gas poisoning and heart failure, the pulmonary lesion in this disease is essentially edematous, and is usually unevenly distributed Urinalysis is helpful in establishing a diagnosis

Acute Coronary Disease. Again the pulmonary changes are similar to those observed in the diseases previously mentioned, and usually are unevenly distributed. The clinical history plus an electrocardiogram should leave no doubt as to the presence or absence of this disease

Acute Lupus It might be difficult to distinguish cases of this disease from some of the cases described by Dr VanOrdstrand,* but as the distribution of any pulmonary lesions is patchy, acute lupus is not easily confused with the usual chronic form of pulmonary granulomatosis

Periarteritis Nodosa The lesions in this disease tend to concentrate in the middle of the lung fields in a more or less definite butterfly pattern, but may be unevenly distributed.

Virus Pneumonia In its clearing stage this disease is the most difficult of all to distinguish from chronic chemical pneumonitis, for at that time diffuse and fairly uniform fine nodules may be observed The linear markings, however, are more prominent than in the latter disease In the early stages of virus pneumonia the distribution of the lesions is patchy

* See Chapter 6 (*Ed*)

Erythema Nodosum In at least one case it has been difficult to distinguish chronic pulmonary granulomatosis from erythema nodosum, which in that case was ruled out only by means of a series of films Erythema nodosum is an acute disease but with a tendency to be a prolonged one.

Parasitosis Involving the Lungs. Parasites usually cause patchy consolidation which is unevenly distributed. The one exception is *Ascaris lumbricoides*, this type of ascariasis may be quite diffuse.

In my experience it is much more difficult to differentiate chronic pulmonary granulomatosis from the following chronic diseases of the lung than from acute conditions

Pulmonary Sarcoidosis. In some of the early cases of our Massachusetts series the disease was originally diagnosed both roentgenologically and clinically as Boeck's sarcoid and in one or two cases this diagnosis was confirmed at autopsy Whether in these cases the pathologic condition was sarcoid which closely resembled pulmonary granulomatosis or whether it was a sarcoid-like reaction in the lung from exposure to beryllium cannot, of course, be proved at this time. Undoubtedly, cases of sarcoid exist in which the roentgenologic picture is so closely similar to that seen in chronic pulmonary granulomatosis that diagnosis is difficult or impossible Usually, however, pulmonary sarcoidosis is characterized by early involvement of the lymph nodes, and in my experience the linear markings of the lung are increased. The distribution of the nodules varies, in many cases they are not uniformly distributed through both lungs The presence of sarcoid lesions in the skin or other organs would be helpful in diagnosis In a series of films, indications of remission or recovery would be illuminating, as both have been known to occur in sarcoid.

Tuberculosis Both acute miliary tuberculosis and the chronic hematogenous type spread from abdominal or mediastinal lymph nodes may be difficult to diagnose, especially if the reaction to tuberculin is negative and the presence of tubercle bacilli cannot be demonstrated. Most cases, however, show a less uniform distribution of the pulmonary lesions than is seen in chronic granulomatosis. Evidence of pleural involvement and the presence of tuberculous lesions elsewhere in the body would be definite differential points. The record of temperature changes and the

leukocyte count might help toward diagnosis, as would a history of exposure to beryllium.

Silicosis. In some stages of silicosis or in some cases, accurate diagnosis is difficult or impossible The usual distribution of the silicotic nodules differs from that of the nodules seen in chronic granulomatosis. Moreover, the silicotic nodules tend to coalesce. Pleural involvement and emphysema at the bases of the lungs are likely to occur in silicosis Susceptibility to tuberculosis is greatly increased, whereas in the disease we are studying, it seems to be slight or possibly even nonexistent

Miliary Carcinomatosis of the Lung There are two recognized types of miliary carcinomatosis of the lung In the retrograde lymphogenous type the nodules are somewhat larger than those formed in chronic pulmonary granulomatosis. They vary in size and their distribution is irregular. The pleura frequently is involved. The hematogenous type of carcinomatosis in the lungs may be difficult to distinguish from the disease with which we are concerned, but only in unusual cases

Siderosis In the siderosis usually seen in mitral disease, the pulmonary lesions may closely resemble those of chronic pulmonary granulomatosis, but usually their distribution is uneven This condition is more or less benign The clinical history and the configuration of the heart should establish the diagnosis The siderosis occurring in iron miners also is benign, and here, too, the distribution of the lesions is different

Fungus Infections The fungus infections most commonly found in the lungs are moniliasis, aspergillosis, histoplasmosis, and coccidioidosis In pulmonary moniliasis, which many observers consider a secondary infection, the lesions in most cases form large patches. As compared with chronic pulmonary granulomatosis, aspergillosis shows less diffuse distribution in the lungs; moreover, the lesions tend to calcify. In histoplasmosis the lesions are relatively large and are unevenly distributed In coccidioidosis the fungus shows some predilection for the bases of the lungs, and the lesions occur in patches.

Diffuse Malignant Lymphoma or Hodgkin's Disease This disease is rarely manifested in the lungs and nearly always is characterized by glandular enlargement.

Benign Pneumoconioses It is possible that at least in some stages, these conditions may produce a roentgenologic pattern similar to that of chronic pulmonary granulomatosis, but in most cases the nodules ap-

pear to be somewhat larger, softer, and more discrete. Their distribution varies. The disability is relatively slight. It must be borne in mind, however, that in some cases of the disease with which we are concerned there seems to be very little disability in spite of marked involvement of both lungs

So-Called Chronic Pneumonia This disease usually differs from chronic pulmonary granulomatosis both in the character of the lesions and in their distribution.

Summary

Chronic pulmonary granulomatosis, or chronic chemical pneumonitis, seems to produce a characteristic roentgenologic pattern, with diffuse, fine, sandy granulation and nodulation Nevertheless, accurate diagnosis requires not only roentgenologic examination but also a detailed history, including the occupational history Serial films and study of all available clinical data may be necessary before a positive diagnosis can be made, and even with these precautions, some errors and failures must be expected.

Discussion

AGRIPPA C. ROBERT, M D *

Dr. Wilson's presentation has been most complete. For the purpose of emphasis, however, and in the hope of stimulating further discussion, I should like to mention several points

1. The fact should be emphasized that with the possible exception of the fine granulation, the roentgenologic pattern by itself does not present a picture sufficiently characteristic to warrant an unequivocal diagnosis of delayed chemical pneumonitis In all cases the roentgenologic findings must be subjected to critical correlation with the symptoms, the physical and laboratory findings, and the occupational history. Moreover, further efforts must be made to determine what constitutes an adequate history of exposure Once such an outline is established, the problem of diagnosis will be simplified. At present we must take care that roentgenologic findings compatible with delayed chemical pneumonitis do not persuade us

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to make mistaken diagnoses in cases of persons suffering from other diseases Perhaps this has happened with the occasional individuals who present few or no symptoms, but whose roentgenograms suggest delayed chemical pneumonitis and who have worked in surroundings presumably productive of the disease



FIG 48 A 22-year-old woman with history of exposure to fluorescent powder The chest roentgenogram exhibits bilateral reticulation, fine nodulation, and prominence of the hilar shadows

Two cases will illustrate this point Both patients worked in the same plant and both handled the same fluorescent powder One patient is a 22-year-old woman who had no symptoms, but whose chest roentgenogram showed bilateral reticulation, fine nodulation, and definite prominence of the hilar shadows (fig 48)

The other is a 37-year-old man who complained of severe dyspnea, cough, fatigue, and loss of weight, and who was found to have secondary

polycythemia, some condition interfering with proper blood oxygenation, and a considerably decreased tolerance of exercise. Except for the extent of involvement and for the more definite nodulation in the second case (fig 49), the roentgenograms of both of these two individuals are quite similar Perhaps in both cases they reflect the changes occurring



Fig. 49 A 37-year-old male with history of exposure to fluorescent powder The roentgenogram reveals a well-defined nodular pattern throughout both lungs.

in delayed chemical pneumonitis I think, however, that I am justified in questioning the diagnosis in the case of the young woman, I wonder whether she may not be suffering from some less ominous disease such as simple sarcoid.

Perhaps the important difference between these two cases is simply the extent of the involvement. That possibility is a proper question for

discussion, for we know that in certain other diseases, particularly silicosis, the roentgenogram cannot be used as a measure of disability

2. I question whether we are justified in classifying the disease according to stages. Perhaps it manifests itself in a given individual in one of several forms, and if so, division into types, granular, reticular, and nodu-

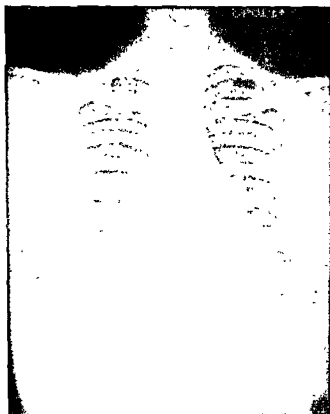


Fig 50 A male, 29 years of age, with occupational history of brief exposure to fluorescent powder The chest roentgenogram reveals a bilateral, fine, sandpaper-like granulation

lar, would be logical It may be significant that in most cases we are unable to demonstrate a definite evolution from one form to another, that there is no clear-cut gamut of stages through which every patient must pass

3. *The following poses another question: is there in some cases a preliminary and perhaps transitory stage preceding what we ordinarily consider the onset of delayed chemical pneumonitis?* This man, aged 29, in November and December of 1942 manually sifted fluorescent powder, and in December became ill with dyspnea, cough, anorexia, and fever.



FIG 51. The same case (fig 50), 10 months later. There is now almost complete clearing of the lung shadows and the roentgenologic picture is considered as falling within the limits of normalcy.

In January 1943 a roentgenogram of his chest showed a bilateral, fine, sandpaperlike granulation or stippling (fig. 50). His symptoms gradually subsided, permitting him to return to work in the same plant, this time as an outside maintenance man X-ray examination showed that his lungs were clearing and by November 1943, 10 months later, the roentgenologic picture could be considered as falling within the limits of normalcy

(fig. 51) After a little more than a year, however, his symptoms recurred Again roentgenograms showed bilateral granularity or stippling throughout the lungs, but this time with a definite tendency toward coalescence in the middle thirds of both lung fields (fig 52) During 18 months of sanatorium care his symptoms remained much the same and his roent-

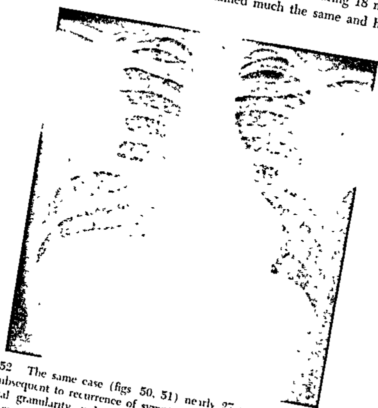


Fig 52 The same case (figs 50, 51) nearly 27 months after fig 50 and subsequent to recurrence of symptoms At this time, in addition to bilateral granularity and stippling, there is definite tendency toward coalescence in the middle thirds of both lung fields

enograms showed that the disease was gradually progressing (fig 53) rom our last report, nearly a year after his discharge from the san- orium he remains totally disabled

The course of this man's disease is unique in our experience We do ow that in most cases however, a considerable time has elapsed ween the beginning of the presumably harmful exposure and the

development of symptoms. Is it not possible that in other cases frequent serial roentgenograms taken before the onset of symptoms might have disclosed a similar and perhaps preliminary phase of the disease? If so, would complete removal of the patients from exposure have prevented the subsequent development of disability? Or is disability the inevitable



Fig 53. The same case (figs 50, 51, 52) taken 45 months after fig 50 By comparison with the previous films, greater coalescence of the shadows in the mid-lung fields can be seen, indicative of the progression of the disease

outcome, once the foundation for the disease has been laid? The answer is probably available through frequent roentgenologic examinations of all exposed personnel, and through careful follow-up studies of patients who appear to recover I have in mind a man whose symptoms have subsided and whose roentgenograms have shown clearing Such patients should be followed up in order to detect indications of possible recurrence or progress of the disease in the absence of continued exposure.

DR HARDY. In our Massachusetts series we have 3 cases of patients who were studied roentgenologically during the onset period closely enough so that we can definitely say that their symptoms came first, and their pulmonary changes later Serial films were made because the physicians in these cases were thinking of pulmonary tuberculosis, not of chemical pneumonitis These patients were watched very closely. The loss of weight and the shortness of breath came first, and later the X-ray pattern, in what Dr Wilson and Dr Sosman call the granular stage

DR ROBERT The last case I referred to was the only one of its kind in our experience at Trudeau, but it makes me wonder whether in some of these cases in which the exposure was relatively slight, there may not be something that goes back of what we ordinarily see

DR AUB In the acute cases we made roentgenograms every month and found that films which preceded the acute attacks showed no indications that the attacks were coming on

DR ROBERT I'm very glad to hear that That's a question that has bothered me for quite some time

DR RICHARDSON I should like to add that the man Dr Robert spoke of is ready for work, he's able to walk a mile two or three times a day, and he feels fine His chest films show that his lungs are clearing from above downward He has returned to normal weight, and considers himself practically cured I want to make one statement about him In his initial attack, which occurred in December 1944, just before he was sent to Trudeau, his temperature rose to 103° and 104° F Fever is not supposed to occur, it is not a characteristic of the preliminary attacks or of the delayed type of pneumonitis This man was not put back to work in the plant after the first illness, but he did live 1000 yards from the fluorescent powder plant

I wish to ask Dr Hardy a question about the 2 cases in which Graves' disease was a complication (I know she has done a huge amount of work in that point) I wonder if she knows what verified the diagnosis The chronic disease resembles Graves' disease so strongly that unless one has had a great deal of experience with chronic chemical pneumonitis, in

some of the advanced cases one could easily make a diagnosis of Graves' disease.

DR. HARDY: In each case Graves' disease was observed during the onset period. The diagnoses of Graves' disease were made before chronic chemical pneumonitis was generally recognized in Massachusetts The basis for the diagnoses was tremendous loss of weight, basal metabolic rates in the range between +40 and +56, and enlargement of the thyroid gland. The X-ray studies were made in the thought that the patients might have pulmonary tuberculosis also. Then their occupational stories were considered It was an unusual onset. Possibly thyrotoxicosis acted as a precipitating cause of the occupational illness.

DR PINKSTON I should like to ask about the procedures followed in other plants. At the Clinton National Laboratory we are rank newcomers in the field We are employing what we hope are thorough procedures for the early detection of the disease, but I should be glad to know what others are doing along that line.

DR. WILSON I can make one comment on that. At the Sylvania Electric Company's plants pre-employment chest films are made of all new employees before they go to work If we find any marked variation from the normal that person is not employed Whether a person with a damaged lung is more susceptible than others to this disease is problematical, of course

All employees in one plant have been examined once a year The examination is not made obligatory, but most of the employees are so interested in the disease that we don't have much difficulty in getting them in once a year We would not have difficulty in getting a large percentage of them in even oftener, if we had the facilities to do the job every two or three months

DR. PINKSTON That's what we're doing—X-ray examinations every three months and other types of check-up every six weeks

DR. WILSON One of the first clinical manifestations of the disease is loss of weight. We have informed all the doctors on the staff of the Salem Hospital that if any of their patients who are employed in the plant are losing weight, we want them sent immediately for chest films We have been able to detect one or two cases in that way.

DR RICHARDSON. In answer to Dr. Pinkston's question on routine: in the powder plant we have developed a routine of chest roentgenograms every six months and physical examinations once a year, and these examinations are compulsory

The vital capacity and weight are checked once a month Any loss of weight is taken up with the personnel department, which determines whether there has been family difficulty, illness, dieting, or any other known reason for the change As a matter of routine any employee who continues to lose weight is given a physical examination even though he may have had his examination only a month or two months before. Sometimes these examinations are very revealing

Occasionally it takes a little detective work to get the significant facts, and sometimes the histories of the people who have lost weight reveal some rather humorous things For instance, in the case of one man who turned out to be negative for the disease, we found out that his wife wouldn't get breakfast for him, and that therefore he was really having only two meals a day That situation was promptly corrected, and the man regained his 10 pounds—7 pounds within one month and the total within two months

We have open minds on whether the roentgenologic signs precede the physical signs or whether the loss of weight and the reduction in vital capacity come first We hope sooner or later to have something on that subject.

MR MORSE I'd like to get a word in here from the standpoint of the poor layman who is trying to run a factory Certain considerations discourage us about periodic mass X-rays One consideration is the cost A second is the terrific disruption in the plant, an X-ray examination takes time, and also a certain degree of privacy, even when you have a machine in your own building A third is that it looks as though in order to pick up these cases the period between X-ray check-ups would have to be very short After we had our mass X-ray survey and the films were interpreted as normal, full-blown cases of the disease showed up within a few months A fourth consideration is absenteeism, when people are not there the designated day we have the problem of follow-up And, finally, there are all the mechanical difficulties of getting a good X-ray machine in the factory dispensary, we have met with some of the technical difficulties Dr Wilson has mentioned.

We have adopted the weight check because it is a more practical measure for use in the plant. We are checking all our employees every month for loss of weight. Absenteeism is a problem, it's true, but generally the same person isn't absent on the designated day for two months in a row. This procedure means that about once a month the registered nurse in our dispensary is checking on every employee in the plant. Besides significant information on loss of weight, we have an additional safeguard· the fact that a trained medical observer sees each employee face to face each month and gets an idea of what each employee is like, of how he behaves. We believe that in the friendly atmosphere that develops after the employees get accustomed to coming into the dispensary and talking to the nurse, our chances of discovering cases is about as good as it would be with a routine X-ray examination once a month. Certainly the method is more practical, less hazardous to the individual, and much less costly both in cash outlay and in interruption of production.

DR. ROBERT. The problem is certainly a difficult one I still believe that there is a great deal to be learned by frequent examinations of various types, including roentgenography.

DR. WARING I should like to ask Dr Hardy about something which might be an important diagnostic point in distinguishing between Graves' disease and this new disease. I refer to loss of appetite in relation to loss of weight The thyrotoxic patient shows good appetite, but in spite of that good appetite, loses weight I want to know whether anorexia isn't a conspicuous symptom of this new disease

DR. HARDY Those 2 cases of Graves' disease antedate my arrival on the scene, but the case records suggest that the patients could eat very heartily and still lose weight. That fact was one of the bases of the diagnosis of Graves' disease

Other patients in the series have all shown anorexia.

CHAPTER 10

Physiologic Aspects

GEORGE W WRIGHT, M D.*

The following data concern the physiologic aberrations which we have been able to observe in 7 chronic cases studied quite exhaustively at Saranac Lake The 6 subjects now living, all men, seem to meet the requirements for a diagnosis of the disease under discussion Two have had skin lesions, biopsies of which showed granuloma and 1 has had an axillary lymph node which showed some sort of granuloma. In 3 cases the diagnosis is not supported by biopsy evidence, but clinically it seems to fit these cases very well In the case of the seventh man the diagnosis was confirmed by postmortem studies

Three chief symptoms have been mentioned by other participants in this symposium and certainly these symptoms were the outstanding ones in this group of 7 men. Without exception these men complained of severe dyspnea on exertion, of loss of weight, and of cough The cough has been variable, but in 2 cases it has been severe, and in 1 it has been so severe that through treatment of the cough the patient has become a narcotic addict.

Our observations on loss of weight and on cough are meager As yet we have not made a careful study of the factors involved in the severe loss of weight Such an investigation should be made, for it might uncover an important clue to the pathologic process in the disease This symptom has been extremely striking, and in our series has occurred in all cases During the patients' stay in the sanatorium, however, we observed no loss of weight except in 1 case These men seemed perfectly capable of eating a normal volume of food In general, the metabolic rate has been normal, the highest rate which we have observed was + 20 per cent.

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Intractable cough has been very distressing. Little or no sputum has been associated with this cough in most instances In the cases in which cough has been severe, *lymph nodes in the hilum have always been* obviously enlarged, when these nodes were not prominent, cough was not a severe symptom.

The third and most disabling symptom is dyspnea on exertion We have made an exhaustive study of this particular problem in our subjects. Among other things, we have studied each man's reaction to increasing stints of exercise This was done by exercising the subject for six minutes on a motor-driven treadmill moving at 3 5 miles per hour, or at a speed suitable for the particular subject. After each work period the grade was increased by 2 per cent until a grade was reached at which the subject could not finish the full six minutes' walk, in other words, a level of energy expenditure finally was reached that caused physical exhaustion in less than six minutes. The ventilation, or volume of air inspired, the *oxygen consumption, and the carbon dioxide output per minute during* the last two minutes of each exercise period were measured. The pulse rate during exercise and recovery was recorded.

Much information can be had at a glance from a graph in which the ventilation per minute per 10 kilograms of body weight is the ordinate and the oxygen consumption per 10 kilograms of body weight is the abscissa of each level of exercise. Figure 54 shows this ratio for one sedentary, 38-year-old, normal male and for the pathologic subjects of this study.

For the human body to expend physical energy it is necessary that the muscles burn fuel, and this combustion requires that the muscles receive a continuous supply of oxygen proportional to the rate of energy expenditure The peak rate at which one can consume oxygen is therefore a good measure of one's maximal ability for sustained expenditure of physical energy. Evidence of this fact is seen in the great contrast between the normal sedentary man's average peak rate of 3 to 3.5 liters of oxygen per minute, and the rate of 5.5 to 6 liters per minute attainable by the very best of middle distance runners, for example, by Don Lash, holder of the world's record for the 2 mile distance *The peak rate of oxygen consumption is a very important index of the body economy.*

In fig 54 the peak rate attained by a normal man, whose rate is characteristic for a group of normal men, is contrasted with the peak rates

attained by 9 men with respiratory disease Subjects 2, 3, 4, 6, 7, and 8 in fig 54 are the patients whose condition is diagnosed as pulmonary granuloma associated with exposure to beryllium Subject 1 is the same person as subject 8, studied after an interval of 21 months. His peak rates, well below the normal range at both times, correspond to the degree of

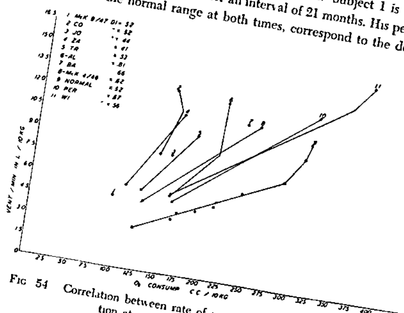


FIG 54 Correlation between rate of ventilation and oxygen consumption at increasing intensities of work

disability as evidenced clinically, the striking deterioration in his performance on the treadmill fits with the deterioration of his appearance and the aggravation of his symptoms If the subjects tested were ranked according to the severity of their physical limitations as observed clinically, the order would be the same as if they were ranked according to their peak consumption of oxygen

Subject 5 is a man whose clinical picture imitates that of the disease under discussion in every way except for loss of weight The question of his exposure to beryllium is so obscure however, because the amounts of beryllium involved were infinitesimal, that I doubt very much that anyone would include him in the same category with those known to have been exposed to beryllium He was a miner for a few months, and then worked in a sintering plant of an iron-mining company Recent samples of the ore handled in that plant have been sent for analysis to

Mr Poritsky, who reports a faint trace of beryllium in the ore. This man's condition makes him unique among literally thousands of people who have been employed in that mine in the past eight years and whose chests have been carefully examined roentgenologically. I call attention to him because in nearly every respect he has exactly the same problem as do the patients with pulmonary granuloma presumably due to beryllium, and he has the same appearance, yet his known exposure has been to amounts of beryllium so infinitesimal that if they are significant, we shall have to conceive of all of us as being exposed to beryllium.

Subject 10 is suspected of the disease under discussion. His exposure to beryllium was of a degree which apparently is sufficient to cause the disease, but, as fig. 54 shows, he is well able to perform on the treadmill, a fact which fits with his relative freedom from symptoms He, therefore, must still be considered merely a suspect.

Subject 11 provides an example of active Boeck's sarcoid with extensive involvement of the lung parenchyma. His high capacity to consume oxygen fits with the scant clinical symptoms. In numerous other cases in which pulmonary parenchymal disease was demonstrated roentgenologically, for example in cases of siderosis, uncomplicated silicosis, and healed pulmonary tuberculosis, the patients have been shown to retain a high capacity for oxygen consumption

The most important information to be gathered from this set of observations is that the pathologic subjects could not supply their tissues with sufficient oxygen to permit their going on to higher levels of work.

We must now consider those mechanisms the failure of which might render the body unable to supply sufficient oxygen to the tissues. First, normal supply of oxygen must be present in the air in the lungs; therefore, failure to ventilate the lungs properly might result in an inadequate supply of oxygen available for consumption by the body. Secondly, oxygen must traverse the alveolar membrane, an obstruction preventing the passage of sufficient oxygen through this membrane would mean that the erythrocytes, the oxygen carriers of the blood, would be inadequately supplied with oxygen

A third type of failure might result from insufficient capacity for transporting oxygen from the lungs to the tissues. that is, from too few red blood cells or too little hemoglobin, or from retardation of the blood flow

through a reduction in the cardiac output or perhaps in the capillary flow in muscles.

Another possible factor, which might or might not be associated with failure of one or more of the aforementioned mechanisms, is the development of intolerable discomfort at low levels of exertion For example, painful arthritis of the knee or hip might seriously limit the maximum level of exertion, and thus might prevent the attainment of a high level of oxygen consumption. Similarly, the development of intolerable dyspnea at low levels of exertion would prevent the subject from attaining a high level of oxygen utilization, even in the absence of other possible causes of such failure

Our subjects invariably have complained of becoming short of breath during exertion To become short of breath during heavy exercise is normal, but to do so during less intense effort is abnormal, and constitutes dyspnea. Dyspnea is defined also as "the awareness of respiratory distress" These men, then, have been alarmed or distressed by becoming short of breath at levels of exertion which formerly were tolerated with complete comfort and total obliviousness of any respiratory effort

Though space does not permit consideration of details, some discussion of the mechanics of dyspnea may help to clarify our understanding of the problem presented by these subjects

The breathing apparatus consists of a mechanical device, which is simply a bellows, and of muscles operating the bellows under the control of the central nervous system. In muscular effort the degree of stress is determined by the ratio of load to capacity For example, in weight lifting the strain on the muscles which perform this task is determined by the ratio of the actual weight lifted to the maximum weight which the same man can lift In the case of the respiratory apparatus, load may be expressed in terms of the ventilation rate, or liters of air inspired per minute, and capacity in terms of the maximum number of liters of air which the same person can breathe voluntarily in one minute. Thus we have a means of measuring dyspnea

$$\frac{\text{Ventilation per minute}}{\text{Maximum breathing capacity}} = \text{Dyspnea index,}$$

$$\text{or } \frac{\text{VPM}}{\text{MBC}} = \text{DI}$$

A normal man lifts a small weight easily, without noticeable stress, but

when he lifts a heavy weight he experiences difficulty and feels a strong sensation of stress, in the latter instance, impulses from the muscles inform the brain of the need for a great expenditure of energy. Similarly, during slight exertion the respiratory apparatus normally does its work without calling attention to itself, but during great exertion gives rise to strong sensations of stress, when the brain is made aware of the need for increased respiratory effort Studies made at the Trudeau Foundation and elsewhere indicate that the normal person rarely becomes conscious of using his breathing apparatus until the load becomes 30 per cent or more *of the capacity.*

The sensitivity of the cortex of the brain, where stress on the respiratory apparatus is measured or interpreted, is an important factor in the problem of dyspnea, for the degree of cortical sensitivity determines the point at which one become aware of respiratory effort Therefore, a complex relationship must be considered which may be expressed as VPM/MBC times cortex. Our studies indicate, however, that in the disease with which we are concerned, a possible increase in cortical sensitivity may be excluded as a major factor in causing the dyspnea As shown in fig. 54, the affected men without exception were able to force themselves to attain a high dyspnea index Moreover, none complained of shortness of breath until this index had reached a value of 0.3 or more

Figure 54 shows that 4 of the 6 men with this disease had sufficient breathing capacity to reach as high a ventilation rate, in terms of ventilation per minute per 10 kilograms of body weight, as did the normal man. Moreover, as has been mentioned, during maximum work each of the 6 attained a ventilation rate resulting in a high dyspnea index. We can conclude, therefore, that 4 were able to call on a normal amount of breathing power during exercise, and also that all were able to drive themselves *to use a normal maximum proportion of their breathing capacity*

The most striking fact is that these men attained high dyspnea indexes at such low levels of work. Our data strongly suggest that the subjects were unable to reach high levels of work output and oxygen consumption primarily because of the intolerable dyspnea which developed at low levels of work This theory is supported by the observation that in most normal men, muscle failure limits the steepness of the grade on which a subject can complete a stint on the treadmill, whereas in the *beryllium*

cases, intolerable dyspnea was as potent a factor as leg weakness in determining the exhaustion level

The question must be raised as to why these men developed dyspnea Obviously, if, at a given level of exercise formerly tolerated without respiratory discomfort, the denominator of the fraction VPM/MBC is reduced or the numerator is increased, or if both these changes occur, dyspnea is likely to develop In other words, dyspnea on exertion can arise from loss of breathing capacity, or from overbreathing in response to exercise, or from both phenomena.

In our studies the maximum breathing capacity, which may also be called the breathing reserve, was determined by the method described by Hermannsen [275] Table XVI compares the determined capacity in each of the 7 beryllium cases with the predicted capacity, an estimate made on the basis of the total volume of the lungs, as calculated from roentgenograms, and on the age of the subject, according to a regression formula developed in our laboratory It will be seen that 2 men, Co and Za, both of whom were subject to severe dyspnea on exertion, proved to have greater maximum breathing capacity than had been predicted In fact, of the 7 men studied, only 2 had a markedly low maximum breathing capacity The large decrease in McK's maximum capacity occurring during a 21-month period is striking, however It is apparent that severe dyspnea on exertion can occur without a loss of breathing reserve When such a loss occurs, however, it clearly increases disability

In the same table, variations in breathing capacity are compared with measurements of the total pulmonary volume and of the residual air after expiration In 3 cases, those of Ma, Jo, and Co, the actual volume of the lungs was significantly smaller than the predicted volume Nevertheless, Co at first showed a normal breathing reserve, although after a 15-month interval a reduction in breathing capacity, associated with a decrease in lung volume, was found More striking is the fact that in McK's case after 21 months a severe loss of breathing reserve was observed, without any measureable loss of total lung volume It appears that in some cases the disease does cause a decrease in lung volume, primarily in space to accommodate complemental air In other cases, however, it produces no measurable change in total volume

Abnormality in the amount of residual air seems more closely related to breathing capacity than is lung volume Four of the subjects showed

TABLE XVI MAXIMUM BREATHING CAPACITY AND LUNG VOLUME CHARACTERISTICS

Subject	*MBC in L air/min*		*Difference as % of predicted MBC*	*Lung vol in L*		*Difference as % of predicted lung vol*	*Residual air as % of determined lung vol*
	Determined	Predicted		Determined	Predicted		
McK	132	150	−12	4.77	4.92	−3	38
McK*	66	150	−56	4.94	4.92	0	60
Co	198	140	+41	3.63	4.87	−25	30
Co†	162	140	+16	2.98	4.87	−39	25
Jo	103	128	−20	3.26	4.45	−27	25
Za	178	157	+20	4.71	5.40	−13	29
Al	102	138	−26	5.47	4.77	+15	50
Ba	124	178	−30	6.08	5.99	+2	37
Ma	54	114	−53	2.79	4.95	−44	39

* After 21 month interval.
† After 15-month interval.

significantly large amounts of residual air in proportion to the total lung volume Three cases showed a normal amount of residual air and of these only 1 had an MBC lower than predicted In the case of McK, the sharp drop in breathing capacity was accompanied by a great increase in the amount of residual air It appears that a reduction in capacity can result either from a severe reduction of the total lung volume, as in the case of Ma, or from the development of a high residual volume, as in the case of McK In general we have interpreted a high proportion of residual air as indicating either a loss of lung retractility, or the "trapping" of air in the bronchial radicles It seems likely that impaired ability to expel air from the breathing apparatus is associated with emphysema

From the data in table XVI we can conclude tentatively that in this disease severe dyspnea on exertion usually is not accompanied by serious loss of breathing reserve (In 2 cases no loss of reserve was suffered) We can also conclude, however, that when breathing capacity does drop, the dyspnea is seriously aggravated

An examination of the numerator in the fraction VPM MBC is illustrated in table XVII To test the normality of the breathing response during exercise, one compares the pulmonary ventilation to energy expenditure Numerous investigators have shown that over a wide range of intensities of energy expenditure the ventilation rate bears a linear relationship to "work " External work done on the treadmill is difficult to calculate, and therefore most investigators prefer to use oxygen consumption per minute as an index of energy expenditure Some possibly serious objections can be made to the use of such an index for extremely high rates of energy expenditure, but fig 54 shows that in the normal man the ratio of ventilation to oxygen consumption was linear over a wide range of levels of energy expenditure

Data which we have not yet published show that for each liter of oxygen consumed in the fifth and sixth minutes of work on the treadmill, 25 liters of air, plus or minus 5, normally are breathed The ratio of air breathed to oxygen consumed is termed the ventilation equivalent for oxygen and may be expressed as O_2V In table XVII, it will be noted that the data for the normal man were taken at a level of oxygen consumption higher than that reached by any of the pathologic subjects. This level, however, is one that in a normal man is well within the range of linear relation between the ventilation rate and the rate of oxygen

TABLE XVII RESPIRATORY AND METABOLIC RESPONSE TO PHYSICAL EXERCISE

Subject	*Treadmill*		*L /min*		O_2V	*DI*	*Clinical dyspnea rating*	*L breathed/min*		*Difference as % ventilation in air*
	m p h	% grade	Air breathed	O_2 consumed				Air	O_2	
Normal	3.5	8.0	51	1.9	27	27	0	51	45	−12
McK	3.5	8.6	81	1.87	44	62	4+	81	63	−29
McK*	1.5	0.0	31	0.66	47	47	3+	33	21	−24
Co	3.0	6.0	84	0.97	86	53	4+	56	35	−34
Jo	3.0	0.0	44	0.86	52	43	3+			
Za	2.0	8.0	76	1.14	66	43	3+	75	50	−33
Al	3.5	8.6	83	1.40	59	81	4+	59	39	−34
Ba	2.5	8.6	82	1.76	47	66	4+	82	51	−38

* After 21 month interval

consumption, hence a comparison of ventilation equivalents should be valid. Compared to the value of 27 found in the case of the normal man, the ventilation equivalent was distinctly high in every other case, and in some cases reached extraordinary magnitude. It should be noted that at the levels of exertion recorded in table XVII, each pathologic subject suffered severe dyspnea, evidenced by the dyspnea index (VPM/MBC) as well as clinically. One must conclude that in this disease, overbreathing definitely occurs during exertion. This abnormality clearly explains the severe dyspnea.

If, in addition to overbreathing, the patient suffers also a loss of breathing reserve, the dyspnea is seriously increased. This unfortunate development is clearly illustrated by the case of McK, whose ventilation equivalent remained essentially constant over a 21-month period, but whose maximum rate of oxygen consumption dropped sharply because of the decrease in breathing capacity.

TABLE XVIII. ARTERIAL BLOOD OXYGEN (IN VOLUMES PER CENT)

Subject	During Rest			During Exercise		
	Oxygen		*Percent of Hemoglobin Saturation*	*Oxygen*		*Percent of Hemoglobin Saturation*
	Content	Capacity		Content	Capacity	
McK	19.9	23.6	84	17.1	24.6	70
Co	20.3	27.7	73	19.3	29.3	66
Jo	13.9	16.3	86	13.3	16.5	80
Za	19.0	23.4	81			
Al	19.3	18.2	82	20.4	24.0	85
Ba	16.7	19.5	92	18.5	19.9	92
Ma	16.6		85			

Some data bearing on the causes of this overbreathing are shown in tables XVII, XVIII, and XIX. Five of the 7 pathologic subjects when at rest have discernible cyanosis of the nailbeds, ear lobes, and nose, and during exercise this cyanosis becomes strikingly exaggerated. Table XVII shows the decrease in the ventilation rate during exercise when the subject breathes pure oxygen (open circuit) instead of room air. The magnitude of the drop is clearly greater in the pathologic cases than in that of the normal man. These data suggest that the overbreathing is due, at least in part, to hypoxia, but they do not indicate the site of the hypoxia

Table XVIII gives the percentage of oxyhemoglobin in the arterial blood at rest and during exercise. The value during exercise was obtained by means of an indwelling needle. With one exception, Ba, the subjects showed a clear deficiency of oxygen in the arterial blood, and in 2 cases this deficiency became astonishingly more severe during exercise. The fact that Ba showed such a minor degree of hemoglobin unsaturation, but did overbreathe, and also breathed less when respiring pure oxygen, indicates that the overbreathing is only partly explainable on the basis of hypoxia.

TABLE XIX GAS PRESSURES* ON EITHER SIDE OF ALVEOLAR MEMBRANE

(Expressed in millimeters of mercury)

during a known rate of oxygen utilization and per cent of arterial hemoglobin saturation

	At rest		During exercise	
	Co	M.K	Co	M.K
CO_2 in arterial blood	28	50	33	51
O_2 in arterial blood	45	60	43	43
O_2 in alveolar air*	108	83	103	80
O_2 gradient	63	23	60	37
O_2 in alveolar air	108	76		105‡
CO_2 in alveolar air†	28	49		31‡
O_2 consumption in L/min	0 29	0 28	0 94	0 66
O_2 saturation of hemoglobin	73%	84%	66%	70%

* Calculated according to the formula of Riley and Lilienthal

$$\text{Calculated alveolar } pO_2 = \text{Tracheal } pO_2 \left(\frac{\text{\% of } N_2 \text{ in expired air}}{\text{\% of } N_2 \text{ in inspired air}}\right) - \frac{\text{arterial } pCO_2}{\text{Exp air R Q}}$$

† Determined by the Haldane method

‡ Determined by the Henderson method from terminal expired air

The dynamics of gas transfer through the gas-blood interface of the lung is illustrated in table XIX. As shown in table XVII one subject had a greater than normal maximum breathing capacity, a significantly diminished total lung volume, and a normal proportion of residual air. In addition, our studies of lung ventilation efficiency (data not presented) showed normally effective ventilation in this case There was no reason to expect low proportion of oxygen in the alveolar air, and indeed, the amount of oxygen in the alveolar air was found by both the Riley and Lilienthal method and the Haldane method to be normal. Nevertheless, the proportion of oxygen in the arterial blood was found to be only

approximately 50 per cent of normal, and the oxygen gradient was about seven times the normal figure During exercise the oxygen gradient was not significantly increased, although the amount of oxygen in the hemoglobin was decreased The low proportions of carbon dioxide in the arterial blood during rest and exercise indicate that there was no obstruction to the transfer of carbon dioxide. It is clear that in this case, as in the cases on* which data are not presented, the oxygen gradient was tremendously increased.

Space does not permit discussion of the various factors which determine the oxygen gradient, but the material presented by Dr. Vorwald makes it evident that in this disease the chief impediment to the transfer of oxygen to the blood lies in the alveolar membrane

The data on McK in table XIX afford an interesting contrast to the case of Co The proportion of oxygen in the alveolar air was found by both the Riley and Lilienthal method and the Haldane method to be definitely low whereas the proportion of carbon dioxide was high In the arterial blood the percentage of oxygen was low, and that of carbon dioxide was high During exercise the amount of oxygen in the arterial blood decreased and the oxygen gradient increased One's first reaction to this information is the thought that in this case the transfer of both oxygen and carbon dioxide was impeded by an obstruction in the alveolar membrane, which in the case of Co impeded the passage of oxygen only In table XVII, however, we find that McK showed a large amount of residual air on expiration, a fact suggesting emphysema In addition, our data show inefficient lung ventilation in this case The latter phenomenon is thought to account for the high amount of carbon dioxide in the arterial blood, whereas an impediment in the alveolar membrane is considered the cause of the high oxygen gradient

Summary

In the disease with which we are concerned, the earliest apparent physiologic abnormality accounting for dyspnea on exertion is an impediment to the transfer of oxygen across the gas-blood interface of the lung This impediment presumably lies chiefly in the alveolar membrane As a result of the obstruction, the pressure of oxygen in the arterial blood is lowered, so that during exercise, overbreathing occurs through abnormally strong stimulation of the chemoreceptors. In virtually every respect the respiratory response of the pathologic subjects in our studies

was identical with that of a normal man exercising at a high altitude. As the disease progresses, lung tissue may be destroyed, with a consequent loss of lung volume, and emphysema may develop These complications further cripple the lung by reducing the breathing reserve and by causing inefficient ventilation of the alveoli. Our data suggest that the dyspnea on exertion at first is due to an abnormal increase in the numerator of the fraction VMP/MBC, but that late in the disease a serious reduction in the denominator increases the severity of this complaint

The abnormal alteration of respiratory action seen in the cases studied is certainly unusual, at least in the degree of its severity, for the forms of industrial fibrosis studied so far at the Trudeau Foundation. The fact that similar abnormalities have been observed in at least 1 case in which the patient had not been exposed to beryllium makes one hesitant to accept the theory that this element or a compound of it is the sole or perhaps even the primary cause of the disease in question.

Discussion

DAVID B DILL, PH D *

Dr Wright's data remind me of the adaptation of the human organism to scarcity of oxygen at high altitudes. Studies made in the Andes revealed one end result, polycythemia. The industrial disease under discussion also produces polycythemia, but it does so in an entirely different manner

At high altitude there is a deficiency of oxygen on the outside of the alveolar membrane The transfer of oxygen through that membrane to the blood is efficient, but until one becomes acclimatized, the short supply results in a deficiency of oxygen in the blood, and a consequent reduction in the capacity for work This deficiency before acclimatization is evidenced by dyspnea, felt especially during exercise, but occurring even during rest. When one is exposed to this condition for many weeks or months, an increase in hemoglobin occurs. The most remarkable subjects studied in the Andes were a group of sulfur miners who lived at an altitude of 17,500 feet and climbed about 1500 feet higher each morning to their work These men showed marked polycythemia,

* Scientific Director, Medical Division, Army Chemical Center, Maryland

with the amount of hemoglobin from 50 to 70 per cent above normal Yet, even so, these men appeared to be in good health, and had good circulatory efficiency

In the cases which Dr. Wright has studied, the cause of polycythemia obviously is increased resistance in the alveolar membrane to the transfer of oxygen from the alveoli to the blood Hence the oxygen saturation of the blood is very much reduced and the response is an increase in pulmonary ventilation, an attempt to surmount the difficulty

It is significant that when one of Dr Wright's subjects was supplied pure oxygen to breathe, the pulmonary ventilation was greatly reduced This fact demonstrates quite clearly that the deficiency occurs in the transfer of oxygen in, and not in the transfer of carbon dioxide out The subject was able to dispose of all the carbon dioxide produced, despite a ventilation of one-half or one-third that observed when he was breathing ordinary air. The dyspnea or the air hunger, therefore, was caused by a lack of oxygen and not by an accumulation of carbon dioxide

Dr Wright's paper strikes me as a remarkably convincing demonstration of the importance of a joint attack on a complicated problem such as this, with many disciplines contributing to the effort, the promise of a solution is greatly increased In this symposium we are to see the evidence brought forth by pathologists Dr Wright has made a brilliant application of the science of physiology The importance of nutritional studies has been pointed out Undoubtedly, the pharmacologists and physiochemists have much to contribute to the study of this disease

Dr Wright's work demonstrates the importance of studying the organism under a load. In the study of a disease of this type, obviously much information is gained by determining to what extent respiratory function is handicapped during the performance of a measured task

Further Discussion

DR SHELESNYAK: Dr Wright, I'd like to inquire whether you have any evidence indicating that the obstruction interfering with diffusion through the alveolar membrane is possibly enzymatic in nature

DR WRIGHT I have no such evidence

DR. DILL: I should think it improbable that the obstruction is enzymatic

CHAPTER 11

Pathologic Aspects

ARTHUR J VORWALD, M.D.*

A discussion of the pathologic manifestations seen in certain beryllium workers might best be introduced by a brief review of some aspects of pneumoconiosis which seem fundamental for a clear insight into the problem confronting us

Pneumoconiosis is a generic term having reference to the pulmonary deposition of dust inhaled into the lungs The term has no implication concerning the pulmonary reaction to that dust To indicate the type of dust, specific terms, such as anthracosis, siderosis, asbestosis, and silicosis, are employed They not only refer to the type of dust but also connote characteristic pathologic reactions in the lungs The reaction differs according to (a) the localization of the particular type of particles, such localization being effected through the activity of the phagocytes, (b) the degree of impairment of the lymphatic system, and (c) the ability of the particular kind of particles to instigate proliferation in the connective tissue Consequently, the pulmonary reaction to dust may be divided into a number of general phases.

1 Early phagocytosis of the dust particles by macrophages
2 Migration of dust-laden macrophages into the alveolar walls of the lungs
3 Drainage of the dust-laden macrophages into the perivascular lymphatic vessels and the tracheobronchial lymph nodes.
4 A mild tissue reaction, consisting of the appearance of phagocytes and of a few inflammatory cells in the air spaces and the septal walls.

* Director, The Saranac Laboratory and The Trudeau Foundation, Saranac Lake, New York

5. Pronounced proliferation of cells about deposits of dust in the alveolar walls, and also in and about the lymphatic trunks
6. Enlargement of the mediastinal lymph nodes through the accumulation of cells and the proliferation of connective tissue

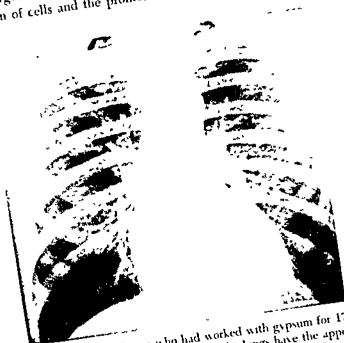


FIG 55 A 57-year-old man who had worked with gypsum for 17 years before his death from syphilitic infection The lungs have the appearance of health, except for a slight exaggeration of the linear markings This exaggeration is known to be due to perilymphatic accumulations of dust-laden macrophages

7. A late chronic tissue reaction consisting of the appearance of inflammatory cells and the proliferation of connective tissue with the formation of a characteristic histopathologic pattern in the parenchyma of the lung

Different phases of the general reaction are accentuated by the action of different types of pure dust Whereas nontoxic dusts such as carbon, gypsum and iron oxide are capable of eliciting only the first four phases in the foregoing list, silica asbestos and other toxic dusts produce all the phases. Figures 55 through 63 provide a pictorial summary of the tissue changes produced by various dusts inhaled into the lungs

These tissue changes are to be contrasted with those found in the lungs and in the tracheobronchial lymph nodes of workers with an occupational history of exposure to beryllium Succeeding paragraphs summarize our observations made at the Trudeau Foundation in the [illegible] of postmortem material submitted to us in such cases

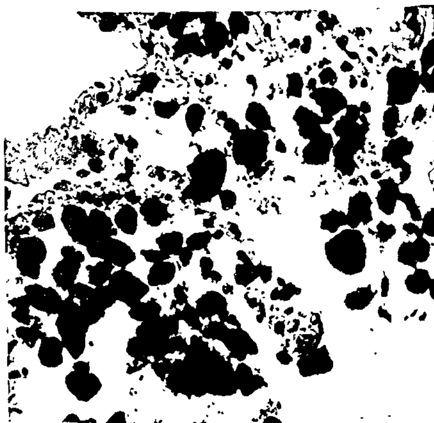


FIG 56 High-power photomicrograph showing alveolar phagocytes loaded with pigment The appearance of such phagocytes is the first reaction to inhaled dust, whether or not the dust is toxic The motile phagocytes tend to cleanse the lungs by carrying the dust into the draining bronchioles, whence it is expelled, or into the alveolar walls and the lymphatic system

The pulmonary disease peculiar to beryllium workers has been variously labeled as chemical pneumonitis, bronchiolitis, metal fume fever, bronchoalveolitis, chemical pneumonia, atypical pneumonitis, delayed



Fig 57 Accumulations of dust-laden phagocytes in the perivascular lymphatic trunks. The dust particles are massed about the vascular channels, not dispersed as they are in fig 59, which shows the reaction to a biologically active dust.



Fig 58 Section of tracheobronchial lymph node with accumulated, black particulate dust within phagocytes, but without significant inflammation A small island of uninvolved lymphoid tissue is recognizable at the top of the picture in the center

Fig 59 Early perivascular reaction to mixed dust containing quartz The black dust particles within *macrophages are dispersed* locally about the central vascular trunk by reason of the focal infiltration of inflammatory cells and the deposition of collagen (compare with fig 57)



These tissue changes are to be contrasted with those found in the lungs and in the tracheobronchial lymph nodes of workers with an occupational history of exposure to beryllium. Succeeding paragraphs summarize our observations made at the Trudeau Foundation in the study of postmortem material submitted to us in such cases

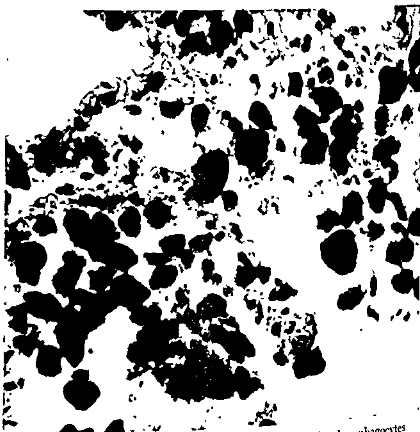


Fig 56. High-power photomicrograph showing alveolar phagocytes loaded with pigment. The appearance of such phagocytes is the first reaction to inhaled dust, whether or not the dust is toxic The motile phagocytes tend to cleanse the lungs by carrying the dust into the draining bronchioles, whence it is expelled, or into the alveolar walls and the lymphatic system

The pulmonary disease peculiar to beryllium workers has been variously labeled as chemical pneumonitis, bronchiolitis, metal fume fever, bronchoalveolitis, chemical pneumonia, atypical pneumonitis, delayed



Fig 62 A cluster of mature silicotic nodules, consisting of concentrically whorled, hyalinized fibrous tissue, in a tracheobronchial lymph node The nodules are the result of local concentrations of quartz particles drained from the lung



Fig 63 A 37-year-old man who had worked for years as a stonecutter This picture shows the characteristic roentgenologic pattern of simple silicosis discrete nodular lesions, which do not exceed 6 mm in diameter, are seen scattered uniformly throughout the lungs

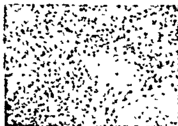


Fig 64 Early pneumonic process in the acute form of the disease observed in beryllium workers The process consists of hemorrhage, fibrination, edema and the exudation of large mononuclear cells and lymphocytes Polymorphonuclear leukocytes rarely are present

chemical pneumonitis, berylliosis, beryllium sarcoid, and pulmonary granulomatosis, with consequent confusion. Many of these terms fail to differentiate the condition from other well-defined pulmonary diseases, and implicate an unproved etiologic agent. Too few of these labels are based upon the pathologic changes in the lung.



FIG 60 Later pulmonary reaction to quartz particles in mixed dust The lesions are discrete and nodular, and consist mainly of large mononuclear cells, histiocytes, and proliferated connective tissue At this stage, hyalinization is less prominent than that caused by pure quartz.

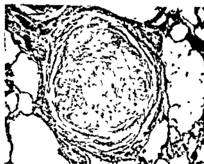


FIG 61. Mature pulmonary lesion due to inhaled quartz This is the typical lesion of simple silicosis It consists of an isolated, well-defined nodule of concentrically whorled, hyalinized fibrous tissue

a pneumonic process For the most part, the process is characterized by capillary engorgement, occasional focal hemorrhage, pronounced edema, and the appearance of cellular exudate and of some fibrin The general absence of polymorphonuclear leukocytes, however, and the preponder-

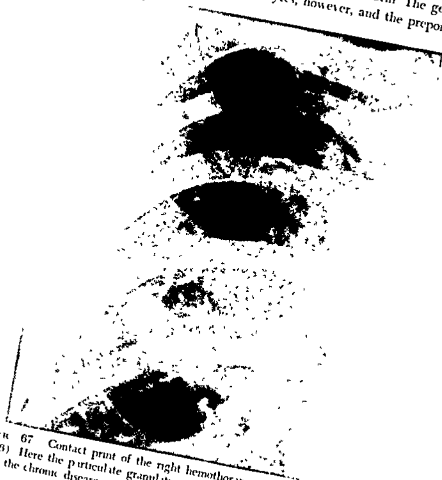


Fig 67 Contact print of the right hemothorax in the same case (fig 66) Here the particulate granulation and the reticulation characteristic of the chronic disease are magnified

ance of lymphocytes, plasma cells, and large mononuclear cells serve to differentiate the acute disease from the changes resulting from pulmonary deposition of any of the most infectious organisms and of many irritating agents Otherwise, the histologic reaction (figs 64 and 65) has no specific characteristics upon which a diagnosis can be based

It is evident from studies previously reported and from contributions to this symposium that this disease may be classified in two distinct forms, the acute and the chronic. Whether one form precludes the other, or whether a relationship exists between the two types, is still debatable.

In the acute form of the disease the pulmonary changes in essence are



Fig. 65. Late pneumonic process in the acute form of the disease. In addition to the general edema, fibrination, and cellular exudation, an appreciable proliferation of histiocytes occurs which thickens the alveolar walls. Often the histiocytes tend to form small focal aggregates not unlike those occurring in the chronic form of the disease. Occasional giant cells also are observed

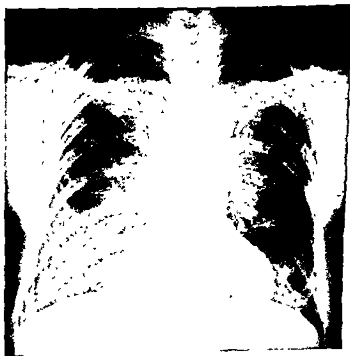


Fig 66 A 59-year-old white male with the chronic form of the disease The patient's only exposure to beryllium occurred during a brief period of experimental work. Both lungs show a general fine stippling or granulation, with a tendency to concentration and coalescence. The hilar shadows are slightly elevated, especially on the left side.

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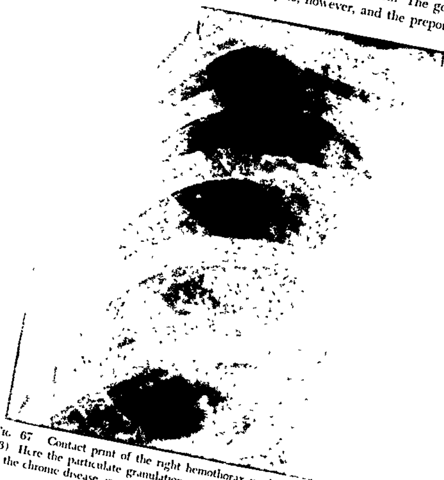


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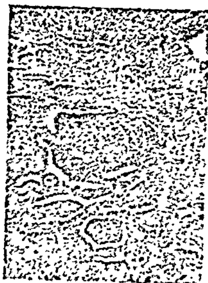


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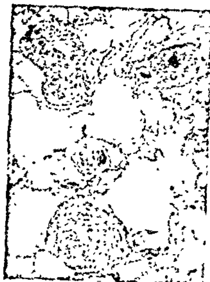


Fig 66 A 59-year-old white male with the chronic form of the disease. The patient's only exposure to beryllium occurred during a brief period of experimental work. Both lungs show a general fine stippling or granulation, with a tendency to concentration and coalescence. The hilar shadows are slightly elevated, especially on the left side.

A



B





C



Caption on facing page

D

Table XX PATHOLOGIC FEATURES OF FOUR TYPES OF PULMONARY DISEASE

	*Pulmonary granulomatosis**	*Boeck's sarcoid*	*Silicosis*	*Tuberculosis*
TYPICAL LESION	Consists of loose aggregate of macrophages and lymphocytes in alveolar walls, producing marked distortion Epithelioid cells, if present, are scattered individually and do not form compact syncytial nodules (epithelioid tubercles) Cytoplasm of monocytes contains much lipid	Consists of compact mass of syncytial epithelioid cells, with collar of lymphocytes Macrophages are rare or absent Lesion produces thickening of alveolar septums with preservation of pattern. Cytoplasm of monocytes and giant cells contains little lipid.	Consists of well defined nodule of whorled, hyalinized fibrous tissue in which are scattered macrophages containing dust	Consists of central zone of necrosis surrounded by epithelioid cells, often radially arranged, with outer zone of lymphocytes. Macrophages occur in some early lesions (especially in experimental animals). Lesion destroys alveolar septums.
GIANT CELLS AND CONCHOIDAL BODIES	Typical Langhans' cells occur, with conchoidal bodies which apparently do not contain elastin.	Typical Langhans' cells found, with conchoidal bodies which take elastic tissue stain	Typical Langhans' cells found without conchoidal bodies.	Langhans' cells with no conchoidal bodies occur usually at margins of lesion

FIBROUS TISSUE	Occurs in very small amounts, in strands. Hyalinization occasionally is relatively pronounced in mature lesions	In healed lesions occurs in typical pattern	Constitutes essence of lesion	Usually circumscribes lesion.
NECROSIS	Occurs in some lesions. Resembles caseation	Absence of necrosis is one of chief criteria for Boeck's sarcoid	May occur in center of the large conglomerate mass	Is characteristic. If necrosis is absent, tuberculosis is not distinguishable from Boeck's sarcoid.
ORGANS INVOLVED OTHER THAN LUNGS	Tracheobronchial lymph nodes affected, and occasionally liver, spleen, bone marrow, and other nodes. Lesion formed by infiltration with macrophages and occasional giant cells. Lesion occurs subcutaneously after direct implantation	Lymph nodes, heart, bone, spleen, etc., develop tubercles †	Regional nodes and occasionally spleen, liver, and bone marrow affected	Any organ may be involved

* Pulmonary granulomatosis in beryllium workers.
† Hyperproteinemia occurs, usually with reversal of albumin-globulin ratio. Blood phosphatase and sedimentation rate are often increased.

one of the early cases For control, the lungs of a healthy man, A-52, who had had no exposure to industrial dust, were analyzed similarly.

At the time these analyses were made, reliable methods for determining very small amounts of beryllium by chemical methods were not



Fig 68 Cross section of the right lung in the same case illustrated in figs 66 and 67 The general thickening of the alveolar walls, and the distortion and obliteration of the air spaces which are characteristic of the chronic disease may be observed The tracheobronchial lymph nodes are enlarged.

available. Although beryllium oxide was reported as "none found" by chemical methods, the spectrographic analyses disclosed some beryllium in the lung tissue of all of the subjects who had been exposed. No beryllium was found in the lungs of the control, A-52.

The values in table XXII are interpretations of the intensity of the lines recorded in the spectrograms. These are arbitrary values, representing only approximate estimates of the amounts of the different elements; they cannot be converted into micrograms per gram of tissue Research is now in progress in our laboratory on methods for determining quantitatively the minute amounts of beryllium in biologic materials, and it is anticipated that reliable procedures, both chemical and spectrographic, will soon be developed

In this table it is interesting to note that the highest values for beryllium were found in cases 297, 322, 338, and 361, all from the fluorescent lamp industry The next highest value was found in case 358, that of a

TABLE XXI CHEMICAL ANALYSES OF LUNG ASH*

Case	BeO	ZnO	MnO	PbO	SiO_2	MgO
A-52	—	—	—	—	0 25	1 70
P-297	NF†	NF	NF	—	0 37	2.10
P-322	NF	0 24	0 07	—	0 49	0 16
P-328	NF	0 20	Tr ‡	—	4 36	2 78
P-338	NF	—	Tr	—	0 69	0 39
P-355	NF	—	0 02	—	9 72	1 98
P-358	NF	NF	—	—	1 32	3 56
P-359	—	—	—	—	0 70	2 28
P-361	NF	Tr	NF	—	0 51	2 09
P-369	—	Tr	NF	—	1 25	2 36

* Values are percentages of the ash in each case
† None found
‡ Trace

woman who had given no history of employment in an industry using beryllium, but had lived a short distance from a fluorescent lamp plant She had ascribed her condition to dust brought home from the factory by her daughter and to dust discharged from the plant into the air

One might suspect that the character and extent of the pulmonary involvement would be related to the amount of beryllium present in the lungs that in case 322, with a spectrographic value of 50 for beryllium, the disease had been most advanced, and that in case 328, with a value of only 5, it had been least advanced Such an assumption is not warranted, however Patient 338, whose lungs showed a spectrographic beryllium value of 30, manifested a more acute type of reaction than

TABLE XXII SPECTROGRAPHIC ANALYSES OF LUNG ASH*†

Case	Be	Zn	Mn	Pb	Si	Mg
A 52	0	3	2	0	50	75
P 297	40	25	8	50	50	80
P 322	50	25	10	25	50	75
P-328	5	25	10	5	50	60
P 338	30	15	5	10	45	30
P 355	20	65	5	30	50	50
P 358	25	10	5	5	50	50
P 359	10	15	5	8	50	50
P 361	30	15	5	12	40	50
P 369	20	50	10	30	15	50

* These values are arbitrary quantities representing line intensities in the spectrograms, they cannot be converted directly into percentages
† For values of other elements refer to tables LXX to LXX [illegible]

either patient 322 or patient 297 Patient 361, whose lungs also showed a value of 30, had exhibited the most advanced type of chronic lesion seen in any of the cases studied. In cases 359 and 328, with beryllium values of only 10 and 5 respectively, the disease had been similarly advanced, revealing extensive fibrosis and hyalinization.

When zinc beryllium manganese silicate is suspect, if the spectrographic value for beryllium is high, then the values for zinc should be correspondingly high This does not appear to be the case, however. Only 2 of the 4 lung specimens from individuals who had been employed in the fluorescent lamp industry showed moderately high values for zinc by spectroscopy, and the quantities detected in the cases by chemical methods were very small. Specimen 355 showed an abnormally high spectrographic value of 65 for zinc, yet this patient had had no industrial exposure to zinc except what might have occurred in the crematory where he had worked, or what might have been due to a neighboring plant using beryllium A sample of crematory ash such as that to which this man had been exposed failed to manifest the presence of zinc, and embalming fluids by law cannot contain salts of heavy metals which might cause medicolegal complications. The small amount of zinc found in the tissues of this patient remains unexplained If zinc were the cause of disease in this case, similar disease should have been detected in some among the thousands of persons exposed to this metal in various industries, but there is no medical record of such disease.

The manganese, lead, magnesium, and silica discovered in the lungs in these cases may be suspect, but no relation between these substances and the granulomatous disease observed in beryllium workers has ever been discovered. No substantial evidence has been found that manganese, lead, or magnesium are capable of causing specific lesions in the lungs. Silica, of course, is capable of causing pulmonary lesions, but the tissue response in silicosis is distinctive

In summary: the chemical and spectrographic values in this disease are proof only of exposure to various mineral substances, they indicate nothing of the character and extent of the associated tissue changes In the light of present knowledge some etiologic significance may be attached to beryllium, but definite proof that beryllium is the causal agent is still lacking.

Discussion

HARRISON S MARTLAND, M D *

In the work of Dr. Vorwald and his associates the Trudeau Foundation is living up to its well-earned reputation as the center for the investigation of occupational diseases of the lungs I therefore want to emphasize the necessity of sending to the Saranac Laboratory all available autopsy material in cases of suspected beryllium poisoning, so that many of the still confusing and controversial problems arising from this elusive occupational disease may be solved.

Just as Koch and others have postulated criteria for determining the existence of disease entities, we medical examiners have established certain criteria for judging cases of suspected poisoning

1 It must be proved that the victim was exposed to a specific poison
2 The symptoms reported must be compatible with the syndrome known to result from the specific poison
3 Autopsy must disclose lesions of the type known to be caused by the poison, and no other cause of death may be found
4 The toxicologist must recover the poison in what is considered a lethal amount

Such criteria are absolutely essential for proper police and court action I feel that these conditions have been met in the beryllium cases The amount of beryllium which constitutes a lethal dose, however, has not been clearly established More autopsy material is needed for study.

To determine the lethal amounts of beryllium in the chronic disease may be difficult or even impossible If the granulomatous nature of the disease is appreciated, one can easily imagine how granulomatous cells, once stimulated by the irritant, might in overcompensation continue to proliferate in the presence of infinitesimal amounts of beryllium embedded in the pulmonary tissues

In 3 of the cases discussed in my paper,† death was due entirely to the pulmonary disease, congestive heart failure resulted from the long-continued pulmonary hypertension It is true that in 2 of these cases, granulomas were found in the liver, but the chronic passive congestion

* Chief Medical Examiner Essex County, Newark, New Jersey
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As to whether we should speak of acute and chronic forms of the disease, I think at the present time we should.

The acute disease seems to be due to concentrated but relatively brief exposure and probably could be prevented by better industrial housecleaning Histologically, it is entirely different from the chronic disease, rather, it closely simulates an organizing virus pneumonia. Whether the acute type of pneumonitis may progress into the chronic is controversial. Some evidence exists that this may occur in a few instances

The chronic pulmonary granulomatosis is an insidious disease of delayed onset, and apparently results from relatively slight but prolonged exposure The disease may be well established even before it is recognized roentgenologically. Symptoms may not occur until long after the patients have left the employment in which exposure occurred

For this reason, as regards compensation, the chronic disease reminds me of our famous experience in New Jersey with radium dial painters. Because radium poisoning was not listed in the compensation laws of the state at that time, none of the victims could obtain compensation Five were forced to take civil action, and after years of wrangling these cases were settled out of court. On the basis of the "statute of limitations" the Supreme Court of New Jersey prevented further civil action by this group of workers because their disease did not manifest itself until two years after they left their occupation I predict that the same thing is going to happen with beryllium workers, unless deaths occur in states in which all types of occupational disease are fully covered by the compensation laws.

Further Discussion

DR. MCCANN· I should like to ask Dr Vorwald whether he examined the thyroid gland in any case

DR. VORWALD. The thyroid was sent us in just one case Whenever possible, we tried to find out how organs other than the lungs were affected but, unfortunately, the material that comes to us is usually only the lung or part of the lung.

DR. HARDY: I should like to ask Dr Vorwald whether he agrees with Dr. Martland that this disease is primarily pulmonary, or if he agrees with me that it is systemic.

DR VORWALD I am sorry, Dr. Hardy, that I cannot answer that question, although we have attempted experimentally to find the answer. I suspect, however, that the disease is pulmonary rather than systemic.

DR SMITH How do you explain the nausea and vomiting that seem to be characteristic of many of these cases?

DR VORWALD. Certainly other pulmonary diseases produce nausea and vomiting

DR DILL. Nausea and vomiting are characteristic manifestations of the anoxia of high altitudes

MR MERRILL Dr Martland raised the question of the safeguards provided in industrial plants In my company's plant for manufacturing fluorescent powder, we are continually making dust counts of the atmosphere to guide our efforts to control the dust The highest concentration now is about 5,000,000 particles of the powder per cubic foot of air, whereas in the past it may have been quite a bit higher than that For the most part the concentration is about 1,000,000 particles or less

We have made every effort to enclose all equipment from which dust might arise and to cover it with hoods, and we provide negative pressure on the equipment and on the hoods, to draw the dust away from the operators and prevent its escape into the atmosphere which the employees are breathing

DR WRIGHT One point which Dr Vorwald and I have often discussed should be mentioned. From the clinical standpoint, I have been struck by the discrepancy between the degree of change visible in the roentgenograms and the extreme disability which some patients show.

Occasionally, one may be misled by roentgenograms suggesting only mild changes even though the patient has severe symptoms In this disease, as in silicosis, one should be cautious in estimating disability from the chest roentgenogram

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CHAPTER 12

Differential Diagnosis

JOSEPH C. AUB, M.D *

It is wonderful how much has been learned about this new disease in the five years since it first attracted attention The disease has been described pretty well, and has been classified in two categories, the acute and chronic A remarkable amount of physiologic and pathologic study has been done, so that we probably understand this disease better, after five years, than lead poisoning was understood during a period of more than a thousand years. That is how well the research seems to be progressing.

I am convinced that a new disease, with acute and chronic manifestations, occurs in the beryllium industry In the course of this symposium I have been further convinced that beryllium plays an important etiologic role I should hate to incriminate beryllium unjustly but, certainly, evidence against it is accumulating. Nine cases in Boston of acute pneumonitis in people exposed only to the purest beryllium attainable and to beryllium oxide are strong evidence that pure beryllium is at fault.

To be perfectly fair I must mention another case, that of a man who worked in a laboratory, and had no exposure to beryllium that I could discern, but who had a typical case of the disease, and a severe one In addition, Dr. Williams reports that a woman who had been exposed only remotely to beryllium had a typical chronic case

The fact still remains that the preponderant important evidence points to beryllium

Our discussions have been muddied a little by confusion in nomen-

* Director, Cancer Commission of Harvard University, Medical Laboratories of the Collis P Huntington Memorial Hospital, Massachusetts General Hospital, Boston, Massachusetts

clature I have been bothered by the words "allergic" and "sarcoid." Because one hears these terms frequently, one unjustifiably assumes that he knows more about the disease if it is called allergic or sarcoid In both the acute and the chronic forms, however, the picture seems sufficiently clear-cut so that the nomenclature should not distract us.

I don't know whether Dr Wright would object to this statement, but the acute form of the disease seems to me to be due to an acute edematous reaction in the lung This reaction is best demonstrated clinically by the diminution in vital capacity In the small number of cases which I have seen, the vital capacity seems to provide the best functional test for an approaching attack In most of the acute cases, intense dyspnea accompanied exertion, but no dyspnea occurred when the patients were at rest

A recent paper on bagasse disease,[202a] by Dr Donald Hunter of London, is illustrated with reproductions of a number of interesting chest roentgenograms Bagasse is sugar cane Workers exposed to its dust get an acute disease with a roentgenologic picture like that in the disease with which we are concerned Hunter reports that the illness lasted a very short time and then was relieved completely, with a general return to normal. He also reports several cases of extensive fibrosis which developed later from bagasse

Other substances may cause acute dyspnea One example is cadmium, which causes tremendous edema in the lungs, and produces a roentgenologic picture something like that associated with beryllium

It has been asked why everyone who has been exposed to beryllium does not get the disease In every disease known to industrial medicine the variation in susceptibility is marked Everyone who has been interested in the lead industry knows that some people can work all their lives and have no manifestation of poisoning, whereas others become ill after short exposure

I remember one fantastic experience involving two women, both of whom were exposed to benzol at the same work bench One died, whereas the other had no manifestation of poisoning The one with no symptoms was an alcoholic, and was hypersensitive to benzol, to which she had been exposed for six years The other who died of benzol poisoning, was a girl of 21 with no bad habits that I know of She had been exposed for six weeks Differences in susceptibility to any disease are enormous

To establish the existence of the new disease as an entity, I do not think it is necessary in the chronic form to find beryllium in the tissues. It is necessary in some given number of cases to prove its presence in the tissues at some time in the patients' histories, but in many conditions abnormalities are produced when the causative agent is no longer present. Some cancer-producing agents, for example, cannot be found in the cancers which they have caused, and some, such as radium, are found in infinitesimal amounts. The amounts are infinitesimal partly because the disease may manifest itself 15 or 20 years after the first exposure. I do not believe that the fact that beryllium has been found only in small quantities in pathologic tissue should influence us too much in our opinion on the role of this element. Nor does the difference in the manifestations of the disease make very much difference.

What appears to bother many people most is the delay in the onset of symptoms. Among those of us interested in cancer, the long lag between exposure and onset is what many of us ponder over much of our time.

In human beings, the phenomena in the two conditions, cancer and this new disease, are not dissimilar. Cancer of the lung in human beings comes only after years of exposure. In uranium mines, Sikl found the earliest tumor developed 13 years after exposure had begun. For 17 years on the average these miners worked without showing evidence of the disease. Radium produces sarcoma of bone 15 to 20 years after exposure.

With the carcinogenic agents the delay in the manifestations of disease may be subjected to experimentation. All carcinogenic agents allow a long latent period before cancer develops. In experiments with mice, the lag may last for a large part of the life of the mouse, it may be a year, and a mouse lives only about 15 months. The neoplasm in the mouse may be produced with a small fraction of a milligram of the carcinogenic chemical, and the carcinogenic agent is hardly ever discernible in the tumor.

The question is how rapidly these carcinogenic agents may produce change, and how long thereafter the change may become manifest. Exposure to the carcinogenic agent pushes the animal toward a pathologic change called cancer. If exposure to the agent is stopped the tissues return to a normal appearance, but eventually some subjects develop a late stage of malignant disease. Cancer may develop long after exposure to the agent has ceased.

Berenblum reported an extraordinary thing which I think may have a bearing on our problem He made only one application of a carcinogenic agent dissolved in liquid paraffin, the animal thus was exposed only for five or seven days A nonspecific substance later was applied to the same area This substance happened to be croton oil which does not produce cancer by itself Yet, a tumor developed in about seven weeks, far faster than if the carcinogenic agent had been applied for a long time. And no matter when he applied the croton oil, even if 16 weeks after a single application of the carcinogenic chemical, the same pathologic changes occurred as would have appeared if he had applied the oil immediately. Berenblum believes that the carcinogenic agent causes mutation in cells, but that the change does not progress to the point of producing tumors until a second stimulus, in this case croton oil, is applied. This second stimulus suggests the "X" substance which Dr Gardner postulated

The same sort of sluggish response can be seen in man in the chronic disease in the beryllium industry, and also in conditions not of industrial origin It is observed in hyperparathyroidism in which, with continuous exposure to excessive hormone, there is a gradual crescendo in the changes in the bones, which progress slowly

Obviously, various stimuli exist which allow a long latent period, tha is, a slow change to a pathologic condition It would be nice to know what the later stimuli are which push cells to various reactions long after the original stimuli have been applied

From my point of view the most interesting aspect of the whole problem of this new disease is the fascinating researches which it makes possible Research is always interesting in industrial problems in which simple substances produce surprising reactions in tissue I believe that the most important results should come not from efforts to see how many cases of the disease can be found, but rather from scientific investigations of mechanisms

Discussion

ARTHUR J VORWALD, M D *

I am glad Dr Aub brought up the question of nomenclature and the confusion that might result from the use of many different terms to

* Director, The Saranac Laboratory and The Trudeau Foundation, Saranac Lake New York

describe a disease entity such as we are studying here. I have tried as much as possible to avoid identifying this disease with beryllium, because I am not certain that the causal agent is beryllium. I am not sure that another factor, as Dr. Gardner so often suggested, is not responsible for this condition. Therefore, I hesitate to identify this disease by a term incriminating a specific substance.

I prefer the term granuloma, suggested by Dr. Gardner. Granuloma means an inflammatory condition perhaps leading to fibrosis Now, it is true that not all cases of the disease lead to fibrosis. Then, too, I am not sure that the acute form is a separate entity, or one which always disappears. I wonder whether this acute disease may not lead to the chronic type.

Dr. Aub mentioned the latent period I am extremely conscious of it, as I am sure all of us are who are studying the disease In our experimental work at the Foundation, we have been aware of the length of the latent period, and for that reason have looked with disfavor on short term experiments Many, although not all, of our experiments with beryllium are long term experiments, the length being limited by the life span of the animals I am sure it is only from long term experiments that we can draw really sound conclusions.

Further Discussion

MEMBER. I should like to ask one question about the postmortem finding. Is there any relationship between the duration of the disease and the extent of the pathologic changes found in the liver? Have more extensive changes been found in the livers of those patients who lived longer?

DR. VORWALD. There is no relation between the duration of the illness and the severity of the disease One patient was ill only 19 days, and yet had a more chronic type of lesion than did a patient ill for 46 days

In my paper* I tried to show there is no relation between the amount of beryllium in the tissues and extent of the disease in the lungs. I agree with Dr. Aub that the beryllium content of the lungs is no index to the character and extent of the disease

We have had material from only one normal individual to test for the

* See Chapter 11 (Ed)

presence of beryllium and in this instance no beryllium was found I urge those physicians who have lung tissue obtained at autopsy, to examine *that tissue chemically and spectrographically for the presence of the* element.

MEMBER: I am interested particularly in the liver, but not especially the lung

DR VORWALD As yet, we have made no chemical or spectrographic analyses of liver In only 1 case of those we studied did we observe the unit lesion in the liver It was a small microscopic lesion

MEMBER I was hoping that the hepatic tissues might throw some light on the question of whether the disease is local in the lungs or is systemic, as Dr Hardy believes If a patient lived long enough, the disease might be carried from the lungs to the liver

DR VORWALD If that were true, some of our patients who were exposed to beryllium for many years and have advanced chronic disease of the lungs, should show liver damage, but we have not found histopathologic evidence of such damage. I do not believe we can make a correlation as yet

DR BARKULIS Apropos of possible liver disease, I should like to mention a preliminary animal study at the Argonne Laboratory We have tried to duplicate the studies of Dr Gardner with rabbits and we also are studying a colony of mice, which have been given the same compounds in suitably decreased doses Although it is very early to draw any definite conclusions, in the livers of mice which were given multiple intravenous injections of zinc beryllium silicate we are beginning to find small granulomata not unlike those described by Dr Martland.

DR VORWALD Wait a year, and see what your animals show then.

DR AUB I want to make a comment on nomenclature. I did not mean to imply that this disease should be called beryllium poisoning, that would be just as unwise as to call it sarcoid

My plea is that we avoid any *name that favors the illusion that the* problem has been solved The disease can be called chronic or delayed pneumonitis or granulomatosis, which are terms meaning that we do not know what the disease is but let us not use a specific name such as an

allergy or sarcoid or beryllium poisoning, for then we might be tempted to sit back and stop work

DR. WRIGHT Those of us who are beginning to write about this disease are in an embarrassing situation Some precedent has been established for each of several names, and I think we should have uniformity.

DR VORWALD: I should like to follow that suggestion If you will allow me, I shall ask certain members of this symposium to gather to discuss nomenclature

DR HERMAN. As has been indicated, the identification of this granulomatosis as beryllium poisoning may be perfectly wicked I sit on the medical board in Maryland which hears claims for compensation for alleged occupational disease We have a schedule act in which beryllium, of course, is not included I am certain, however, that at the next meeting of the Maryland legislature, beryllium is going to be included. In that case, with the problem as it stands now, our board is going to be on the spot

DR. MARTLAND: The only suggestion I can make at the present time is that the acute disease be known as acute chemical pneumonitis, and if you want to add "beryllium" in parentheses, with a question mark, it is all right with me. The chronic form might be known as delayed chemical pneumonitis, again with "beryllium" in parentheses with a question mark.

Apparently, some of you do not want to believe the disease is beryllium poisoning. I may be sticking my neck out, but I am going on record now to the effect that in the cases in which I have performed autopsies the disease was beryllium poisoning

The comparatively large amount of beryllium (3 to 4 mg.) found in the organs in one case, in which the patient died some four years after exposure, is sufficient to convince me, the beryllium should not have been there.

DR PRATT. I wish to ask Dr. Aub a question He spoke of delay in the onset of disease after exposure to toxic agents, and suggested we should not worry too much about the delay in this particular disease He cited tumors, which are self-propagating once they get started I think that the disease with which we are dealing, however, is an inflammatory one, and

it seems to me that the toxic agent would still have to be present when lesions develop

I want to ask whether Dr. Aub has ever seen an inflammatory disease that developed after exposure to the toxic agent ceased, or one in which the toxic agent was absent at the time of the development of lesions

DR AUB I should like to think about that question I don't know what you mean by "self-propagating" disease Cancer is a manifestation of a change of function in certain cells, the change is manifested pathologically only after it has progressed a long way The disease we are discussing is a manifestation of a change of function in certain cells, it is a reaction to a stimulus

DR VORWALD You might say that a biologic change occurs The resulting abnormal cells may act as an irritant

DR AUB MacLane and Bloom demonstrated the functional change of osteoblasts in the laying hen Normally, the same cells which are osteoblastic at one time, when the bone is deposited, become osteoclastic, breaking up the bone, when the egg has to have a shell These are cells which normally, and repeatedly, change their function

I do not see why other cells cannot change their function when given the proper stimulus Cells change their function insofar as they divide indefinitely when they form a neoplasm

CHAPTER 13

The Chronic Disease in Neon Tube Workers

O A. SANDER, M.D.*

Two cases of chronic pulmonary disease demonstrate that a hazard exists in the neon sign industry, probably because of the use of fluorescent powders. The roentgenograms of both patients show the pattern typical of the disease observed among fluorescent lamp workers. One patient is under my care, and the other case will be described in a medical publication by Dr Reginald Smart of Los Angeles Several other cases, not yet authenticated, have been reported from various parts of the country in the neon sign industry.

The patient whom I have under observation first came to my attention in August 1946. This man, Richard S , now 29, had worked in various neon sign shops since 1936 Before 1938, however, only gases (argon and neon) were used in neon tubing. After fluorescent powders containing beryllium came into use in 1938, this man helped to mix and prepare the powders in a shop run by his two brothers Here he could have been exposed to powder in the air through any of several operations. (1) Powder was mixed with alcohol, and the mixture strained through cloth. Lumps left in the cloth were dried and then shaken out in a cardboard box, with resulting dissemination of dust (2) Dried powder mix was heated in crucibles at temperatures as high as 2300° F., with consequent fumes and dust (3) One one day a month, old tubing was reclaimed by brushing it out During this operation dust was visible in the air This man definitely was exposed from the spring of 1939 until February 1941 During the next two years he worked in numerous neon sign shops as a tube bender, but did no further powder mixing In 1943 he entered the Army Air Corps, and served for over two years. During this period of

* Consultant, Milwaukee, Wisconsin

service several chest roentgenograms were made, none of which were reported as abnormal After his discharge from the Army in October 1945, he returned to work in neon sign shops, where he believes he suffered little or no exposure to the fluorescent powders

In February 1946 he first noted a cough and shortness of breath on

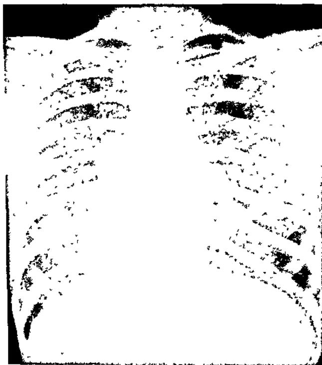


FIG 69 Roentgenogram of a neon sign tube worker It reveals fine discrete stippling throughout both lungs

exertion, which increased during that spring and summer In September he was forced to stop work altogether, and did not return to work until February 1947 Since then he has worked on his brother's farm

In September 1947 he felt much improved He slept better than formerly, had no cough, and experienced shortness of breath only when climbing stairs In general he felt well

This patient's roentgenograms show fine discrete stippling throughout

both lungs, with no areas of confluence No roentgenologic changes occurred between September 18, 1946, the time of his first film (fig 69), and July 19, 1947, the date of his most recent one (fig. 70).

His three brothers also were examined roentgenologically. Their chests were found to be clear, even though two of the brothers had had much

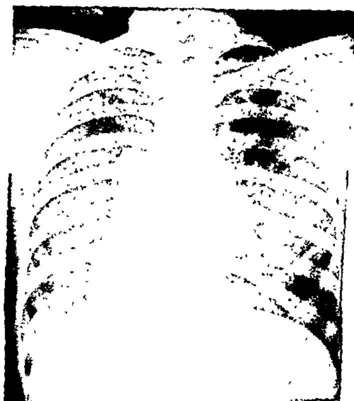


FIG 70 Same subject (fig 69), taken 10 months later.

greater exposure to fluorescent powders than had the man who was affected.

The patient under Dr Smart's care has a history of considerable exposure to fluorescent powders This man is failing rapidly, he is in a state of extreme anoxemia and requires oxygen almost continuously. After his death postmortem studies will be made.

The danger to health in the neon sign industry is increased by the fact

that the industry includes many small shops in which dust control is unheard of

In my opinion, people who work with fluorescent powders should be examined roentgenologically before starting on the job and periodically afterward, if more cases are to be discovered before the disease has reached an advanced stage

Discussion

MR PENNYBACKER My company supplies neon sign manufacturers with coated fluorescent tubing and with some of the fluorescent chemicals used. A considerable number of neon sign manufacturers coat their tubing by what we call 'home" or "kitchen" methods They are absolutely unaware of the importance of getting rid of the dust In such shops the fluorescent materials are used without any binder, whereas in most of the larger plants in which tubing is coated, a binder is used which prevents much dust from coming off These smaller sign manufacturers sweep the floors and dust the powders around.

There are more than 2000 small plants scattered through the country, which make neon signs out of fluorescent tubing Probably about 10 per cent of these manufacturers coat the tubing themselves, under conditions such as Dr Sander and I have described, and such practices have been going on for about seven years

DR VORWALD Dr Sander expressed his anticipation of postmortem studies of one of the patients cited I cannot let the occasion go by without stressing the fact that when postmortem material is available, the Trudeau Foundation would appreciate receiving a supply of that material, sufficient not only for microscopic study, but also for chemical analysis and for experimental study

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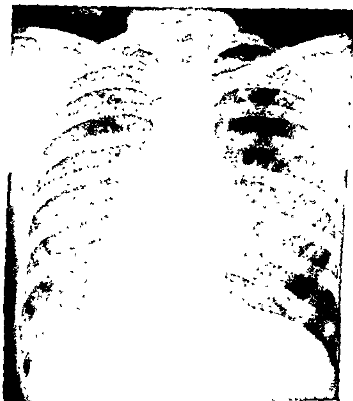


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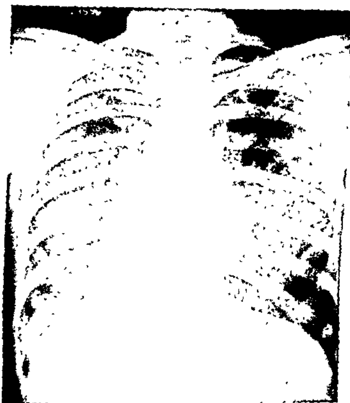


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CHAPTER 14

Postmortem Observations in Cases in Which the Patients Had Been Exposed to Beryllium

HARRISON S. MARTLAND, M.D.*

As far as I have been able to ascertain, New Jersey has had no recorded deaths from industrial beryllium poisoning, except possibly in the following 4 cases of pulmonary disease These deaths came to my attention because the duties of the Chief Medical Examiner of Essex County, N. J., include the investigation not only of violent deaths and others in which crime is suspected, but also of deaths due to industrial diseases and poisonings

Case Reports

Case 19 Chronic Beryllium Poisoning Versus Nickel Poisoning in 1936

This case was referred to me by Dr Raphael Pomeranz of Newark, N J., for autopsy. Dr. Pomeranz summarized the case as follows:

The patient, a white male aged 23, was an industrial chemist exposed to mercury, antimony, and lead His work included boiling nickel in carbon tetrachloride.

He first complained of substernal pain and of loss of appetite and weight These symptoms were followed by a nonproductive cough and shortness of breath, and later by cyanosis and by clubbing of the fingers

Roentgenograms showed fine, diffuse nodules, like millet seeds, scattered over both lungs No calcification or cavitation was observed All tests for tuberculosis gave negative results

The patient was seen by several outstanding physicians, who made the following diagnoses disseminated type of lymphoblastoma, Hodgkin's disease, miliary carcinomatosis, bronchiolitis obliterans, possible obscure occupational disease due to dust Pulmonary sarcoid was not mentioned, as at the time most clinicians were not sufficiently alert to the sarcoids.

Extensive irradiation of the chest was the only treatment that gave

* Chief Medical Examiner, Essex County, Newark, New Jersey

dyspnea. She had been treated by another physician for one year for heart disease. When Dr. Slavin examined her, the roentgenograms showed fine nodulation throughout both lungs, and cor pulmonale. Clubbing of the fingers and marked cyanosis were noted. The results of all tests for tuberculosis were negative. The patient was seen by several New York specialists, who made the following diagnoses: miliary carcinomatosis, Hodgkin's disease; miliary tuberculosis; silicosis, Boeck's sarcoid Dr Slavin was of the opinion that she had some unusual occupational lung disease, but he could elicit no definite history of exposure, it was not learned until after her death that she had worked in the fluorescent lamp industry.

Dyspnea became so extreme that during the last year of her life the patient was constantly under an oxygen mask. She died from congestive heart failure about three years after the onset of symptoms.

Autopsy Extensive bilateral nodulation suggesting fine silicosis or sarcoid, was found in the lungs The walls of the right ventricle of the heart were hypertrophied to a thickness of 9 mm. Chronic passive congestion of the liver, spleen, and kidneys, and also clubbed fingers, were observed

Microscopic examination The pulmonary lesions were of the same type seen in case 19, but no granulomas were found in the liver.

Comment A specimen of lung tissue was sent to Dr. Gardner, who wrote to us as follows.

> Its appearance is practically identical with that of the histology in the first of the so-called Salem sarcoids which came to autopsy. Both [illegible]
>
> on the basis of the latter, and probably assumed the presence of a noncaseating tuberculosis as the cause of the other lesions

This case again illustrates the difficulty of recognizing chronic beryllium poisoning unless one has been alerted to the disease, since so outstanding an authority as Dr. Gardner would not have diagnosed the condition correctly except for the fact that he was studying the Salem cases at the time

Case 21 Acute Beryllium Poisoning in 1947

This case was reported to the Medical Examiner for investigation as possibly one of chemical pneumonitis if not of virus pneumonia.

The patient was a white male, aged 22, with no history of exposure to occupational hazards before he began work in the phosphor department of a fluorescent lamp company Chest roentgenograms made when he started on this job showed no signs of disease For 31 days he was a mill

operator, loading and unloading fired and unfired phosphor powder on the night shift Respirators were supposed to be used in this work On the last of the 31 days the patient complained of pains across his chest, and was laid off the job Two days later, when he was admitted to a hospital, he showed marked dyspnea and cyanosis and complained of weakness and chest pains

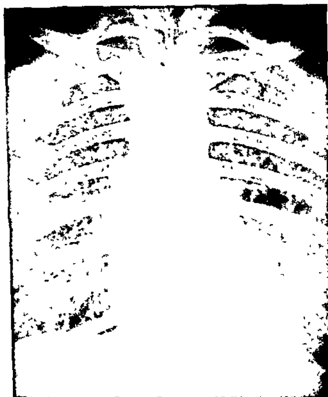


FIG 71 Extensive bilateral diffuse bronchopneumonia in a case of acute beryllium poisoning (case 21)

In the hospital the course of his illness was that of bilateral bronchopneumonia, with little fever, no leukocytosis, and no pathogens in the sputa X-ray examination (fig 71) showed extensive bilateral bronchopneumonia He died 22 days after the onset, modern pneumonia therapy not having influenced the course of his disease

Autopsy The roentgenologic observation of extensive bilateral bron-

chopneumonia was confirmed at autopsy. The lungs were almost solid, and were dripping blood Cut sections usually sank in water. The cut surface was shaded from grayish red to dark red, and showed organization, marked edema, and hemorrhagic extravasation. The left lung weighed 1600 gm., the right lung, 1800 gm.



FIG 72 Tissue specimen from case 21, ×250, showing organizing bronchopneumonia Note the nuclear debris and the absence of polymorphonuclear leukocytes

Microscopic examination. Under the microscope the inflamed tissue (*fig 72*) showed an exudate of plasma cells, lymphocytes, and large mononuclear cells in the alveoli and the interalveolar septums, with a striking absence of polymorphonuclear leukocytes. There was extensive fibroblastic organization of intra-alveolar and interalveolar exudate Squamous cell metaplasia of the epithelium of the alveoli and terminal bronchioles, and large areas of hemorrhagic infiltration, were seen.

Toxicologic examination Examinations by our toxicologist, and also

by the Kettering Laboratory at the University of Cincinnati, showed small amounts of beryllium in the lungs and liver The silica content of the lungs was normal The Kettering analyses, made by that laboratory's newly developed spectrographic technic, disclosed the following amounts of beryllium



Fig 73 Reticulation and snowstorm effect, without evidence of calcification or cavitation, in a case of chronic beryllium poisoning (case 22). Note the prominence of the pulmonary artery, indicative of pulmonary heart disease

In 100 grams of wet lung	20 micrograms
(Total amount in the lungs	0 68 milligrams)
In 100 grams of wet liver	4 micrograms
(Total amount in the liver	0 04 milligrams)

Comment The clinical course and the roentgenologic and autopsy observations in this case were similar to those in the cases of beryllium

pneumonitis described by VanOrdstrand[626] and others in 1945. The microscopic appearance of the lungs was exactly what Goldblatt described in the VanOrdstrand report.

The amounts of beryllium found in the lungs in this case were small, and might signify no more than exposure. So little toxicologic information has been gathered as yet in such cases that the lethal dose, in either the



FIG 74 Portion of a roentgenogram in case 22 enlarged to show the reticulation and snowstorm effect

acute or the chronic form of beryllium poisoning, cannot be determined with accuracy at present. Some authorities therefore might question the diagnosis of beryllium poisoning in this case, and might attribute death to an organizing virus pneumonia, which undoubtedly the disease closely resembled Against such an explanation, however, are the occurrence of 38 cases of chemical pneumonitis, with 5 fatalities, in the Cleveland plants producing beryllium copper, and the low mortality in virus pneumonia

Case 22 Chronic Beryllium Poisoning in 1947

This case was reported to the Medical Examiner as one of occupational disease In a civil suit begun before the patient's death, the illness was described as uranium poisoning contracted while the patient was working in atomic research.

This patient was a white female, aged 31 *Before 1942 she was a sales-*
342 she was
cuum with
apparatus
after it had cooled a black smudge settled over her face and in her nostrils At such times she coughed and felt a choking sensation

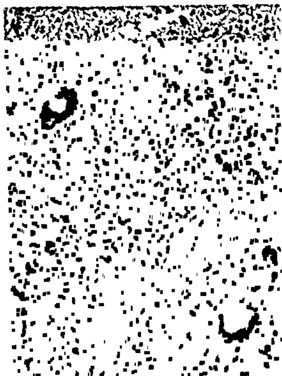


Fig 75 *Tissue specimen from case 22, ×250, to show beryllium granulomas Note the epithelioid tubercle with lymphocytes, large mononuclears, and giant cells This lesion is virtually indistinguishable from Boeck's sarcoid.*

After this three-month period, until 1946, her work was drawing beryllium wire and sheet metal, exhausting tubes, and brazing and soldering Toward the end of 1944 she developed a nonproductive cough and became short of breath By the end of 1946 she was so weak and so short of breath that she had to give up work

From this time on she became progressively worse, with marked

dyspnea, insomnia, and loss of weight Her lips and fingernails were cyanotic, and the fingers were clubbed

Roentgenograms (figs 73 and 74) showed fine nodulation throughout both lungs, producing a reticulate pattern and a snowstorm appearance. The hilar nodes were not unduly enlarged The pulmonary artery was



FIG 76 A giant cell, ×1600, found in a pulmonary granuloma in case 22 The cell contains an inclusion body.

prominent Electrocardiograms showed deviation of the right axis of the heart.

A diagnosis of delayed chemical pneumonitis was made by Dr I. L Applebaum of Newark Tests with a sensitive Geiger counter showed no abnormal radioactivity No beryllium was found during life in the urine, blood, or feces, but accurate tests for the element had not yet been developed

Toward the end, the dyspnea was only relieved by constant administration of oxygen Cardiac failure of the congestive type set in. Enlargement of the liver, edema of the ankles, and slight ascites were noted The patient died five years after exposure to beryllium compounds, and three and a half years after the onset of symptoms

Autopsy Chronic, diffuse, bilateral, interstitial pneumonitis was observed, with innumerable noncaseating, noncalcifying nodules from 1 to 5 mm in diameter Discrete and confluent nodulation throughout the

lungs was seen. Compensatory emphysema was found in most of the lung tissue, all cut sections floated The right lung weighed 720 gm, the left lung, 620 gm Cor pulmonale was manifested by hypertrophy of the walls of the right ventricle to a thickness of 7 mm. Chronic passive congestion was noted in the liver, spleen, and kidneys

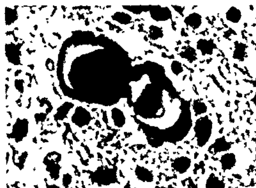


FIG 77 Ringlike extracellular bodies, ×1600, found in a pulmonary granuloma in case 22

Microscopic examination The nodules scattered throughout the lungs usually had centers of epithelioid cells, surrounded by lymphocytes, plasma cells, monocytes, and many giant cells, the last-named containing foreign bodies Virtually no polymorphonuclear leukocytes were found, and no eosinophils The hilar nodes showed the same type of granulomatous lesions, and also larger hyaline nodules somewhat resembling silicotic nodules The general picture (fig 75) was identical with that seen in Boeck's sarcoid Many of the giant cells (fig 76) contained large inclusion bodies, often ringlike, sometimes almost like protozoa. These bodies were stained a deep purple by hematoxylin. Extracellular bodies (fig 77) similar to the inclusion bodies were seen in the granulomatous lesions

Cultures and inoculated guinea pigs showed the lungs to be negative for tubercle bacilli and other pathogens

Toxicologic examination. Spectrographic analyses by the Kettering Laboratory gave the following results

Lungs .	12	micrograms beryllium per 100 gm of wet tissue.
Liver	8 4	" " " " " " " "
Spleen	4 3	" " " " " " " "
Bones	13 5	" " " " " " " "
Kidneys	27 2	" " " " " " " "

With the weights of these organs considered, their beryllium content can be estimated roughly as follows.

Lungs	0.162 mg
Liver	0.134 "
Spleen	0.0086 "
Bones	2.7 "
Kidneys	0.1 "

Comment. In the symptoms and the course of the illness, and in the autopsy and histologic findings, this case is similar to the so-called Salem cases of chronic pulmonary granulomatosis, as reported by Hardy and Tabershaw.[264]

The toxicologic examination in this case was the most thorough one made so far in any of the beryllium cases. The large amounts of beryllium found in the skeleton suggest that although death in such cases is due to the lung lesions beryllium is distributed through most of the body, that after inhalation or ingestion of fumes and dust (the latter often of colloidal size), the metal is deposited in the reticuloendothelial system, as are lead, radium, and arsenic. The disease therefore must be systemic.

The large amount of beryllium found in the kidneys, some 5 years after exposure, suggested the possibility of a urine test which during life will show beryllium in sufficient quantities to form the basis of a diagnosis, and indeed, the Kettering Laboratory has recently developed such a test.

CONCLUSION

On the basis of a study of the foregoing cases, of the VanOrdstrand report on acute beryllium poisoning, of the Hardy and Tabershaw report on chronic beryllium poisoning, and of the work of the late Dr. Gardner,[220] who conducted experimental investigations by injecting beryllium compounds into animals, I have reached the opinion that the existence of industrial beryllium poisoning is well established.

Discussion

DR. WARING. I should like to ask whether industry is making any effort, and if so with what success, to follow up discharged employees, inasmuch as the chronic form of pneumonitis seems to appear several years after exposure has ceased. Is it possible that the disease occurs among discharged employees but is not recognized because the patients are treated by uninformed practitioners?

DR SCORNAVACCHI: Recently, now that the problem has confronted us, the Beryllium Corporation of America has invited former employees to return for examination, and some of them have done so Fortunately, those whom we have been able to follow up are negative for the disease so far

DR SHIPMAN: All the patients who came to my attention did so as a result of leaving their former employment and seeking employment in our plant, for a while the former employees of other companies were quite a fruitful source of cases

I know that the past employers of these people have made reasonably thorough efforts to track down cases It must be remembered, however, that no one in the industry realized that we had a real problem on our hands until after many workers had scattered to the four winds Many of the girls married and moved away, and the young men went into the Army or Navy, so that an intelligent attack on the problem became nearly impossible Nevertheless, much was accomplished, and I believe that more will be done

MR MORSE Sylvania is one of the companies which has attempted to follow up cases arising among former employees The magnitude of that problem is terrific Exposure occurred during the war years when we had thousands of employees, including high turnover groups such as housewives working for patriotic reasons and young girls Naturally, we lost track of most of these people We did approach the Army and Navy in the hope that through their medical work they could track down any cases among our employees in the service, but that search has not been very productive

One thing which has baffled us is the fact that in the past year or so new cases almost without fail have arisen among people who were no longer in our employ, in many instances for several years Dr Hardy has been of real service in helping us find these cases

As a result of meetings such as the one which Mr Bowditch organized in Boston several years ago, and of symposiums like this one, more physicians are becoming aware of the symptoms, so that word of new cases does come back to us Our company has been criticized in the past for talking about our cases From the beginning, however, we have known that we could not possibly track down all the exposed people by ourselves, therefore, we gladly made our experience public in the hope that

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word of it would get to more sanatoriums and physicians, to help them recognize cases The Saranac Laboratory, among other agencies, already does a good job in identifying the disease when cases come up.

Therefore, although we haven't tracked down all of the thousands of people who worked in our plants during the war—some for a few days or a few weeks—we are becoming more hopeful that as this peculiar disease becomes better known, active cases will not be lost.

DR WILLIAMS: *From time to time we see information on the amounts of beryllium found in various human organs Can you tell us what is normal, Dr. Martland?*

DR MARTLAND. As far as I know, no beryllium should be found in normal persons who have not been exposed to beryllium

In the acute case* which I described, the beryllium found amounted to only 20 micrograms in the lungs and 4 micrograms in the liver, per 100 gm of wet tissue. These are small amounts, and inasmuch as the pulmonary lesions resembled those of organizing virus pneumonia, the findings might be interpreted as indicating only that the patient had been exposed to beryllium In one chronic case,† however, about 3 mg. of beryllium was found in the body, and I believe that this was a lethal amount in this case.

DR VORWALD· I should like to refer Dr. Williams again to my paper reporting on chemical and spectrographic analyses of lung tissue ‡

DR. SANDER. Dr. Martland reported the presence of a lot of beryllium in the bones in one case In the Los Angeles case which I mentioned, a biopsy specimen of bone marrow showed no beryllium. I suspect that the element was found in the bone marrow in your case, Dr. Martland

DR. MARTLAND. I am unable to say whether the beryllium was present in the cortex, the marrow, or in both, but because the disease was chronic in this case, I suspect that relatively larger amounts were deposited in the cortex rather than in the cancellous bone. for such has been my experience with radium poisoning Because of the extreme difficulty of determining beryllium analytically, I do not believe that a marrow puncture would furnish sufficient material for a satisfactory analysis.

* Case 21
† Case 22
‡ Chapter 11

DR. DENARDI. In my company we have not endeavored to follow up normal individuals who have left the plant without having developed pneumonitis I have been very successful, however, in following up cases of pneumonitis I have been able to contact more than 70 per cent of the people who recovered from pneumonitis and to have x-ray check-ups made. In all the cases followed up but one, recovery has been complete with only slight residual effects That one patient died of carcinomatosis originating in all probability in the right kidney, death occurred two and one-half years after full recovery from a severe attack of pneumonitis.

We have made no attempt to follow up unaffected employees for the simple reason that during the war years most of our employees were transients, coming from that area of the south including Kentucky, West Virginia, and Tennessee. Only a few of these people remained on the job for more than six months.

DR MILLIGAN· I wonder whether lungs are becoming available for examination from workers who were exposed to beryllium for a period of years but died of other causes If one finds a given amount of beryllium in the lungs of someone who died of a pulmonary condition, the inference is that the beryllium caused the disease In the case of an exposed person who dies of another cause, do the lungs contain the same amount of beryllium which they might if death had been due to pulmonary disease, or are they free of beryllium? Is that a logical question?

DR MARTLAND I have no information on workers exposed to beryllium who have died from causes other than beryllium poisoning Quite possibly the lungs in some cases might show traces of beryllium, but I should not expect to find amounts comparable to those found in the case I described The amounts necessary to establish the fact of poisoning by beryllium compounds have not been determined with any accuracy.

DR VORWALD Your question, Dr Milligan, is a most pertinent and a very important one Unfortunately, the dearth of evidence prevents us from answering it I urge, therefore, that every effort be made to obtain postmortem material from cases in which the patients were exposed to beryllium, even when the cause of death is not pulmonary Not a case of exposure should be missed

DR MILLIGAN· The beryllium industry should be most productive of such cases.

PART FOUR

The Beryllium Problem

Toxicity Studies in Connection with Atomic Energy Production

CHAPTER 15

Introduction

JOE W. HOWLAND, M.D *

To anyone with an elementary knowledge of nuclear physics, and particularly to those whose curiosity was sufficient to prompt the digestion of the Smyth report released by the Manhattan District, the role of beryllium and its compounds in the production of atomic energy is obvious It was only natural that considerable research and developmental work, both physical and physicochemical in character, should be initiated and continued into the present. As early as the beginning of 1946. it was realized that the development of such programs, even on a relatively minor scale, meant that human beings would be exposed to beryllium, with possible toxic effects; the medical division of the then-existing Manhattan District knew that the potential hazard of beryllium might be a very real one, endangering not only industrial personnel, but also irreplaceable scientific personnel Therefore, an experimental program on the toxicity of beryllium and its compounds was deemed necessary

The toxicologic research groups of the organization were consulted for the purpose of formulating a suitable program. Programs then were authorized both in the Metallurgical Project, now the Argonne National Laboratory, and in the Rochester Project. On January 1, 1947, these programs were taken over by the Atomic Energy Commission without major change, and for practical purposes the administrative changes can be forgotten.

From the outset it appeared that the beryllium problem was a nut which would be extremely difficult to crack The funneling of all possible information into the research laboratory was considered necessary. Re-

* Chief, Division of Medical Services, Atomic Energy Project, University of Rochester, Rochester, New York

views of pertinent literature, however, were extremely confusing and of little help Reviews of analytical methods, which up to that time had seemed adequate, revealed extraordinarily numerous faults.

The chronological development of our program at Rochester has a certain interest, as shown in the papers presented here. Our desire, of course, was to organize the program on a sound basis, using the best possible procedures and technics *As a preliminary step, therefore, all* possible efforts were made toward the development of new analytical methods and procedures. The early results of this work are described by Dr Neuman *

Another necessary part of the program entailed field surveys in the plants and areas in which beryllium poisoning of human beings had been observed during the past five years or so. The dust and fumes of the various compounds of beryllium as well as of the metal itself were critically examined by the most modern and up-to-date methods, some of which were developed in our laboratory. A small portion of the results of these studies is now ready for release, and is described by Mr. Laskin.†

While the new procedures which were obviously necessary were being developed and standardized, certain pilot experimentation was under way. These experiments, planned according to standard toxicologic practice, required the exposure of animals (of a total of seven species) to compounds of beryllium administered by all possible routes, that is, by intravenous, intraperitoneal, and intratracheal injection, and by inhalation Certain cutaneous tests were carried out on sensitive species in order to give us some idea of the skin pathology.

In these pilot experiments, the investigators wished:

1 To produce in animals lesions similar to those found in human beings after toxic exposure.
2 To get a tentative idea of the general character of beryllium poisoning and of mortality rate.
3 *To develop certain clinical* and laboratory test methods which would be of value in identifying such poisoning These methods include the determination of weight and loss of weight, respiratory

* See Chapter 22 (*Ed*)
† See Chapter 23 (*Ed*)

tests, analyses for chemical concentrations as well as microscopic examination for formed elements in both blood and urine

4 To answer certain pertinent questions concerning the possibility that infectious and other agents and other toxic materials might act with beryllium in producing the lesions characteristic of human beryllium pneumonitis

To my mind the work which these experimenters have done so far definitely indicates a need for a deeper investigation into the mechanism of beryllium poisoning It is not enough to know whether certain compounds are toxic, and if so, in what concentrations, to know the signs and symptoms of the toxic manifestations, and the possible routine methods by which a hazard in an industrial area can be reduced In our experiments with uranium and its compounds, a better understanding of the toxicity of that element came when we had gained some knowledge of the mechanism of uranium poisoning, especially because this knowledge came through studies by biochemists and cytologists rather than through routine testing procedures Most of our group share my personal conviction that an all-out attack must be made on the problem of the mechanism of beryllium poisoning in both its acute and chronic forms

I can not emphasize too strongly the fact that all the work reported here by members of our group is preliminary in nature Because of the unique security requirements of our organization, only work done before July 15, 1947, when the papers were presented for security clearance, is reported Since that time additional work has been carried out along the same lines and a number of findings have been made It is the wish of the investigators, however, that many of these recent observations should not be made public, because they are only tentative, and because tentative observations so often are completely misinterpreted

CHAPTER 16

Biochemical Studies of Workers Exposed to Beryllium

J. J. NICKSON, M.D.* AND ELAINE J. KATZ, M.A.†‡

In the studies reported here, an attempt was made to detect evidence of subclinical metal poisoning in some members of the Argonne National Laboratory who had been exposed to varying amounts of beryllium Such studies appeared pertinent in view of the evidence which has been produced to show that exposure to beryllium for a protracted period may lead to a peculiar syndrome in human beings[12, 261]

The biochemical problems selected for routine investigation were chosen after much previous experimentation in the attempt to find tests *which would be useful in detecting early damage in men exposed to small* amounts of potentially dangerous metals The tests described here are essentially those reported in detail by Schwartz.[542]

In studies of beryllium poisoning in rabbits, it was shown[543] that liver dysfunction occurred, as indicated by an increased urinary excretion of urobilinogen following the subcutaneous administration of beryllium chloride ($BeCl_2$) in amounts of 0 5 to 1.0 mg. per kilogram of body weight For this reason, liver function tests were particularly emphasized in our biochemical studies made with human subjects. Though the data given in the following pages are not in any way conclusive, the question of systemic damage, either with or without acute illness from exposure to dusts of beryllium or its salts, is of sufficient importance to warrant further investigation Because our investigation cannot be continued at *the Argonne National Laboratory at this time, it seemed* worthwhile to

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† Associate Biochemist, Medical Division, Argonne National Laboratory, Chicago, *Illinois*

‡ With the technical assistance of Manervia Martin.

record the results in the hope that the study of this problem might be undertaken elsewhere. For this reason this note is presented, the authors being fully aware of all insufficiencies

The problem of interpretation was complicated for us by the fact that members of the Laboratory's staff were rarely, if ever, potentially exposed to one toxic agent only Probably answers to the questions raised in connection with exposure to beryllium can be sought more profitably in laboratories or plants where exposure to beryllium is the sole or major hazard

Materials and Methods

Subjects and Specimens

A total of 70 subjects was studied Fifty of these persons worked principally with beryllium Previous intermittent exposure to potentially dangerous chemicals, to other metals, and occasionally to radiation, were, however, complicating factors Ten of the subjects were people who were newly hired or who had not worked with beryllium, and so could serve as controls The possibility of exposure to toxic agents other than beryllium existed for this group Ten controls with no known exposure to any dangerous chemicals or metals were selected from students of one of the liberal arts departments of the University of Chicago No serum studies were made with the last-named group

From each subject, two consecutive 24-hour urine samples were collected in chemically washed glass bottles The subjects spent the two days at home, thus as far as possible the complicating factors of an active working day* and the possibility of incomplete samples were avoided Blood was drawn on the morning of return to work All analyses were made with individual samples Coproporphyrin isomer analyses were made with combined two-day samples of urine

Atmospheric Levels of Beryllium

Sampling of the air in areas where beryllium was being used in general [in]dicated levels of less than 1 microgram of beryllium per cubic meter [of] air Occasional determinations as high as 400 micrograms per cubic [me]ter were obtained, however

* Actually, samples taken at work may be of great value in studying borderline [abno]rmalities, and should be used for certain types of tests

Tests Performed

Porphyrin Metabolism Urinary Excretion of Coproporphyrin: The amounts of the individual coproporphyrin isomers as well as the total amounts of coproporphyrin excreted were determined fluorometrically The procedures used for both the *quantitative estimation of the total* urinary coproporphyrin and of the coproporphyrin isomers I and III were in accordance with methods described by Schwartz and *others*[644]

Liver Function The serum cephalin cholesterol flocculation test of Hanger[260] was employed along with the urinary urobilinogen test of Watson[547] and the thymol turbidity test of Maclagen[391] These tests lack etiologic specificity, but are useful for screening purposes

Serum bilirubin determinations were made according to the method of Evelyn and Malloy,[181] with 0 5 cc of serum used instead of plasma. Previous studies in our laboratory indicated that for routine determinations with normal subjects, there was little to be gained by making tests for both direct and indirect reacting (total reacting) bilirubin, therefore, only the total reacting bilirubin was determined in this study.

With *samples of 1 cc each, the same test was applied to urine;* thus, the material capable of the diazo reaction was measured in terms of bilirubin. This test is not specific, but elevated values routinely are found in instances of known bilirubinuria

Excretion of urorosein-like pigments. Urorosein is a red compound formed by the oxidation of indoleacetic acid, if present, when a mineral acid is added to urine. Its exact clinical significance is unknown, but its excretion appears to be most commonly associated with dietary deficiency[61,84]

The following method was used to extract the urorosein-like pigments *Five cc. of glacial acetic acid are added to 50 cc* of urine This is extracted three times with ethyl ether, using approximately 100 cc of ether each time and shaking in a separatory funnel The combined ether extracts are mixed and then divided into two equal parts One part (Fraction A) is extracted in a separatory funnel with successive small portions of 25% HCl until the HCl extract is "colorless." Only 2-3 cc of HCl are used for each extraction. The final total volume should be 20 cc. One cc of 1% KNO_2 is added to the other part of the ether extract (Fraction B) and is shaken with it This is then extracted with 25% HCl, as above Fraction A is the so-called unoxidized fraction; fraction B, the so-called oxidized fraction.

The light absorption of each fraction was quantitated with the Evelyn photoelectric colorimeter, first with a filter for a wave length of 400 millimicrons and then with a 520 millimicron filter. In the earlier studies each solution was next examined with a pocket spectroscope, and the presence of absorption bands was noted.

About half of the samples discussed in this paper were quantitated with a Coleman spectrophotometer. Readings were taken at wave lengths of 410, 490, 520, 540, and 600 millimicrons in order to determine the absorption pattern precisely. Only readings at 410 and 520 millimicrons are reported in table XXVII.

It should be emphasized that the so-called urorosein fractions include not only urorosein but also urobilin and numerous other pigments, mostly unidentified. The quantitative procedure is therefore not specific for urorosein, although the absorption band at 543 millimicrons appears to be fairly specific for that chemical.*

Scoring System

As an aid in the interpretation of some of the data, the results of several of the tests were graded in categories designated as 0 to 4+. A score of 1+ was questionably elevated, and scores of 2+ to 4+ were increasingly elevated above the usual control values. It should be borne in mind, however, that scores of 3+ or 4+ in these studies rarely were associated with clinical complaints.

TABLE XXIII URINARY EXCRETION OF COPROPORPHYRIN

Number of subjects	μg (per 100 cc)					μg (per day)	
	0	1+	2+	3+	4+	*No above normal**	%
Laboratory workers exposed to beryllium (50)	74	12	8	1	0	17	34
Nonexposed laboratory workers (10)	18	2	0	0	0	3	2
University students (10)	9	1	0	0	0	1	1
Total determinations†	101	15	8	1	0	21	

* One hundred micrograms per day was considered the normal maximum.

† In most instances samples from each person were examined on two consecutive days. Occasionally only one 24-hour sample was examined.

* Though urorosein has an absorption band maximum at about 543 millimicrons as viewed spectroscopically, its absorption in the Evelyn colorimeter was found to be greater with a 520 filter than with a 540 filter. This phenomenon is due to the relatively greater total absorption of the shorter wave lengths as compared to those greater than 543 millimicrons.

The range of values[542] corresponding to each of the scores used is as follows:

Urine coproporphyrin (table XXIII).

0 = <8 micrograms per 100 cc. of urine
1+ = 8–10
2+ = 10–13
3+ = 13–18
4+ = >18

The normal maximum is about 10 micrograms per 100 cc. of urine and 100 micrograms per day. A value of 111 to 140 micrograms per day may be rated as 2+.

TABLE XXIV SERUM CEPHALIN CHOLESTEROL*

Number of subjects	0	1+	2+	3+	4+	*Subjects with 3+ and 4+ values as % of total*
Exposed to beryllium (50)	11	8	4	14	13	45
Nonexposed (10)	4	1	2	2	1	5
Total determinations	15	9	6	16	14	

* Normal serum with known negative reactions, from a laboratory worker, was used as a check in all serum studies

Cephalin cholesterol flocculation (table XXIV): The grades 0 to 4+ were based on degree of flocculation, as described by Hanger.

TABLE XXV THYMOL TURBIDITY

Number of subjects	0	1+	2+	3+	4+	*Subjects with 3+ and 4+ values as % of total*
Exposed to beryllium (50)	22	13	8	3	4	12
Nonexposed (10)	7	0	2	1	0	2
Total determinations	29	13	10	4	4	

*Thymol turbidity** (table XXV):

0 = 100–90° reading of Evelyn colorimeter
1+ = 89°–85°
2+ = 84°–80°
3+ = 79°–75°
4+ = <75°

* This method of scoring thymol turbidity is based on unpublished observations of the reactions of numerous hospital patients and normal men

Serum bilirubin and urine "bilirubin" These factors were not assigned any scores because no considerable variations from normal were observed

TABLE XXVI. URINARY EXCRETION OF UROBILINOGEN

Number of subjects	0–2 49 mg /day	2 5–5 0 mg /day	More than 5 0 mg /day*
Laboratory workers exposed to beryllium (50)	96	3	0
Nonexposed laboratory workers (10)	20	0	0
University students (10)	10	0	0
Total determinations	126	3	0

*Only 3 values were higher than the normal of 2 5 mg per day and none of these was unusually elevated

Urine urobilinogen (table XXVI) According to Watson and Schwartz* normal urine urobilinogen values are usually 0 to 0 5 mg per 100 cc of urine and 0 to 2 5 mg per day Values much greater than these may be considered abnormal

Light absorption with a 400 millimicron filter (table XXVII)

For a 100 cc. specimen of urine

0 = 100 –35° reading of Evelyn colorimeter

1+ = 34°–13°

2+ = <13°

For a 50 cc specimen of urine†

0 = 100–70 reading of Coleman spectrophotometer

1+ = 69–60

2+ = 59–40

3+ = 39–30

4+ = <30

Light absorption with a 520 millimicron filter

For a 100 cc specimen of urine

0 = 100 –55° reading of Evelyn colorimeter

1+ = 54°–35°

2+ = 34°–17°

3+ = <17°

* Personal communication

† The change in amount of urine used corresponded to the change from the Evelyn colorimeter to the Coleman spectrophotometer

TABLE XXVII. URINARY EXCRETION OF UROROSEIN-LIKE PIGMENTS

Subjects	Unoxidized fraction of urine										Oxidized fraction of urine									
	With 410 mμ filter					With 520 mμ filter					With 410 mμ filter					With 520 mμ filter				
	0	1+	2+	3+	4+	0	1+	2+	3+	4+	0	1+	2+	3+	4+	0	1+	2+	3+	4+
Laboratory workers exposed to beryllium (50)	49	39	7	0	0	78	12	3	0	0	40	33	17	5	0	13	23	22	29	6
Nonexposed laboratory workers* (10)	10	8	2	0	0	17	2	0	1	0	9	4	7	0	0	1	8	8	2	1
University students* (10)	5	2	3	0	0	8	1	0	1	0	4	3	2	1	0	4	0	3	3	0
Total determinations	64	49	12	0	0	103	15	3	2	0	53	40	26	6	0	18	31	33	34	7

* The beryllium-exposed subjects showed somewhat greater pigment excretion in the oxidized samples than did the controls, as evidenced by increased absorption at 520 mμ

For a 50 cc. specimen of urine*

0 = 100–85 reading of Coleman spectrophotometer

1+ = 84–70

2+ = 69–50

3+ = 49–35

4+ = <35

Results

The results of the biochemical studies of urine and serum are shown in tables XXIII to XXVII

According to Evelyn, 0 7 mg per 100 cc of serum is the normal maximum for serum bilirubin In these studies, 1 0 mg per 100 cc was considered the normal maximum Six of the subjects exposed to beryllium had values higher than 1 0 mg per 100 cc, with an average of 1 20 mg per 100 cc None of the controls showed a value greater than the normal maximum Although the high values were not indicative of clinical abnormalities, they did indicate a slight trend All 6 specimens with somewhat high values had a definite pink color, indicating a relatively intense diazo reaction

Urinary diazo-reacting substances were not indicative of any abnormalities

Discussion

The interpretation of the findings in these studies is difficult, even in cases of decidedly abnormal values The differences between the value ranges shown by the several groups of subjects often were not considerable Moreover, the exposure of the 50 laboratory workers to toxic substances was potentially multiple and the degree of their exposure to beryllium is only vaguely known

Although lacking etiologic specificity, biochemical studies such as these may be of value for screening purposes Abnormal values would indicate the need for more intensive study of the particular subjects who show such values The results of tests such as these must be interpreted largely on an individual rather than on a statistical basis, interpretation is possible only *with the aid of carefully compiled case histories of past clinical* complaints and of possible exposure to toxic materials. Histories are especially important when the subjects are, or have been, exposed to

* The change in amount of urine used corresponded to the change from the Evelyn colorimeter to the Coleman spectrophotometer

TABLE XXVIII REPRESENTATIVE FINDINGS OF BIOCHEMICAL STUDIES

Subject*	Date	Thymol Turbidity		Cephalin cholesterol	Urine bilirubin		Serum bilirubin	Urine urobilinogen		Urine coproporphyrin			Urine volume	Sp Gr	Uroerythrin-like pigments: In unoxidized urine fraction		In oxidized urine fraction	
		Units	Score		mg per 100 cc	mg /day	mg per 100 cc	mg per 100 cc	mg /day	µg per 100 cc	µg/day	Score†	cc/day		410 mµ filter	520 mµ filter	410 mµ filter	520 mµ filter
L P ♂	1-14-47	2.15	3+	3+	0.12	2.16	0.60	0.10	1.84	8.0	144.0	1+	1800	1.020	0	0	1+	2+
					0.24	4.23		0.02	0.54	5.6	98.7	0	1800	1.015	0	0	0	2+
	4-23-47	2.90	4+	1+	0.29	4.30	0.72	0.05	0.90	2.9	43.0	0	1482	1.013	0	0	0	0
								0.04	0.59									
	6-20-47	2.00	2+	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
R L ♂	1-14-47	2.10	2+	4+	0.33	2.28	0.32	0.05	0.42	14.8	96.1	3+	880	1.030	1+	0	1+	3+
					0.09	0.82		0.08	0.52	12.8	116.3	2+	650	1.030	1+	0	1+	3+
	6-20-47	3.35	4+	3+	—	—	—	—	—	—	—	—	—	—	—	—	—	—
S J ♂	1-16-47	4.98	4+	0	0.38	6.73	0.72	0.03	0.50	5.0	88.5	0	1770	1.027	0	0	0	3+
					0.20	3.90		0.03	0.53	1.2	23.4	0	1950	1.011	0	0	0	1+
	6-20-47	2.46	3+	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
S M ♂	4-23-47	0.95	0	4+	0.26	3.40	0.48	0.04	0.52	9.6	125.8	1+	1310	1.015	1+	0	2+	4+
					0.10	1.67		0.03	0.50	4.6	76.8	0	1670	1.010	0	0	0	3+
	6-20-47	0.75	0	3+	—	—	—	—	—	—	—	—	—	—	—	—	—	—
F P ♂	5-9-47	0.72	0	3+	0.01	0.04	0.24	0.02	0.09	1.6	6.8	0	430	1.030	1+	0	0	1+
					0.43	1.81		0.02	0.08	1.5	6.3	0	420	1.030	1+	0	1+	2+
	5-25-47	0.32	0	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C D ♂	5-23-47	0.92	0	0	0.64	3.01	0.58	0.06	0.28	6.4	30.5	0	470	1.030	1+	1+	2+	2+
					0.36	3.28		0.06	0.54	2.9	26.4	0	910	1.020	0	0	2+	3+
A G ♀	5-19-47	0.82	0	1+	0.26	4.01	0.60	0.03	0.46	6.4	98.6	0	1540	1.015	0	0	1+	2+
					0.26	2.34		0.04	0.36	6.0	54.0	0	900	1.024	2+	3+	2+	3+
	5-25-47	1.05	1+	1+	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* The first 4 persons were from the group exposed to beryllium, the last 3 were chemists with no exposure to beryllium.
† Based on micrograms per 100 cc

minute amounts of more than one toxic agent, in such cases, the exposures on the present job may be secondary in importance to other factors.

The urine urobilinogen values showed no significant elevation, nor did the urine "bilirubin" tests The method used in this laboratory for the determination of urinary diazo-reacting substances is not well enough established to permit interpretation of slight deviations from the normal.

Urinary coproporphyrin values greater than 100 micrograms per 100 cc of urine were found in 17 tests, or 14 per cent of those made with the group exposed to beryllium, but were found in only 3 tests, or 2 per cent, of those made with the nonexposed group Data published by Schwartz[342] indicate that human beings exposed to certain metals commonly excrete an increased total amount of coproporphyrin The values of 3+, or more than 140 micrograms per day, found for 3 subjects, were not strikingly high In only one case (that of L P) was such a value associated with other significantly high values for thymol turbidity and cephalin cholesterol (See tables XXVIII and XXIX)

TABLE XXIX CORRELATION OF ABNORMAL VALUES*†

	No subjects with abnormalities	Same subjects with other abnormalities				
		Coproporphyrin‡	Urorosein-like pigments§	Cephalin flocculation	Thymol turbidity	Serum bilirubin
Coproporphyrin	3	3	1	2	1	0
Urorosein-like pigments	26	1	26	12	4	1
Cephalin flocculation	30	2	12	30	4	3
Thymol turbidity	8	1	4	4	8	0
Serum bilirubin	6	0	1	3	0	6

* Values of 3+ and 4+
† The subjects in this table include all staff members studied
‡ Values greater than 140 micrograms per day
§ In oxidized urine fractions examined with a 520 millimicron filter

In the studies of pigment excretion, the beryllium-exposed subjects showed somewhat greater pigment excretion in the oxidized samples than did the controls, as evidenced by increased absorption at 520 millimicrons This absorption in the oxidized samples calls for further study to see whether any specific urinary compound is responsible for the increased absorption

In all cases the specific gravity and volume of the urine were within the normal range.

Seven beryllium-exposed subjects showed elevated thymol turbidity. Four of these persons also had elevated cephalin cholesterol values, and 1 person had elevated urinary coproporphyrin excretion as well. One other elevated thymol turbidity value was found in a chemist not exposed to beryllium.

Numerous 3+ or 4+ values were also found in the cephalin cholesterol determinations. Because of the number of high values, duplicate analyses were made and, in general, the agreement between the two sets of results was good. All the control specimens of serum from persons with known negative reactions showed normal values.

In the future, serum specimens which show abnormalities in tests for thymol turbidity and cephalin cholesterol flocculation should be subjected to electrophoretic analysis to determine the nature of the serum protein abnormalities.

An analysis of the clinical condition of 4 persons who had been exposed to beryllium, as compared with that of 3 nonexposed laboratory workers, showed no clear-cut differences. Though in the exposed group the incidence of colds was slightly greater than in the control group, though several subjects complained of nondescript symptoms suggestive of influenza and though one or two incidents of inflammation of the eyes were reported, the composite clinical picture suggested only a slightly greater incidence of abnormalities than in the control group.

Representative biochemical findings are given in table XXVIII. All 4 of the beryllium-exposed subjects scored 2+ or more in either the test for thymol turbidity or the cephalin flocculation test, and 3 of the 4 scored 1+ for urinary coproporphyrin. In the group of 3 controls, however, only one 3+ value was found in either of the first two tests and no high values were found for coproporphyrin. With the same 7 men, coproporphyrin determinations were made with eight-hour urine specimens taken while the subjects were at work. This second series of tests gave values of 100 micrograms per day or more for the 4 beryllium-exposed workers, but none for the control group. The tests for serum bilirubin, urine "bilirubin," urobilinogen, and uroroscin showed no differences between the beryllium-exposed group and the controls.

Although individual abnormalities were found with respect to thymol

turbidity, cephalin cholesterol, urine coproporphyrin, urine pigments, and serum bilirubin, none of the tests gave consistently high values for any individual. This fact suggests that the repeated finding of slight abnormalities may be more significant than high values in all the various tests. The greater incidence of abnormalities in the beryllium-exposed group suggests possible systemic damage.

Summary

Clinical laboratory studies of workers exposed to varying amounts of beryllium were carried out for a period of one year with the object of detecting and evaluating possible systemic subclinical metal poisoning. The possibility of systemic damage due to beryllium was investigated primarily by means of liver function tests.

Individual abnormalities were found with respect to thymol turbidity, cephalin cholesterol flocculation, urine coproporphyrin, urine pigments, and serum bilirubin, but no type of test made showed consistently high values for any individual.

Interpretation of the results of the tests is difficult because of the number of toxic materials, of which beryllium was but one, which might have been acting on any given subject.

Under such circumstances, the results of such tests must be interpreted largely on an individual basis rather than on a statistical one, and must be considered in relation to detailed case histories, which are especially important when the subjects may have been exposed to minute amounts of various toxic substances.

Liver function tests and tests for urinary pigments and coproporphyrin fall into the category of screening tests, of value in the study of large groups. The finding of abnormal values for any individual in the group would indicate the need for further intensive study of that individual.

Discussion

FRIEDRICH W. KLEMPERER, M.D.*

The results of Dr. Nickson's tests are highly interesting. I consider it very much worth-while to compare data on people who have been

* Head, Department of Biochemistry, The Trudeau Foundation, Saranac Lake, New York

exposed to beryllium but are not clinically ill with data on patients suffering from the chronic pulmonary disease. I am especially interested in Dr. Nickson's studies of liver function because occasional laboratory data on patients with the chronic disease indicate some disturbance of liver function.

The data which I am giving here on such patients are not new. Most of the information was supplied to me by Dr. Hardy or was gained in studies made of patients at the Trudeau Foundation

In cases of the chronic disease the laboratory findings have been striking essentially because of the absence of abnormal values Only occasional findings have been made that might be interpreted as indicating damage to the liver.

The amount of serum phosphatase is commonly used as a measure of liver function, and I know of only 2 cases in which it was increased beyond the normal level—moderately in one case and slightly in the other. How this fact is to be interpreted is rather doubtful

We are dealing with a very small group of patients, and any conclusions as to the causes of the phenomena noted in the laboratory are certainly not warranted at this time It is interesting, however, that one patient with a kidney stone showed a serum calcium level of 11.7 mg per 100 cc. and also an increase in the serum phosphatase

One observation has been made in more than one or two cases. a rather striking increase in the serum globulin It is unfortunate that in the early days the disease was regarded as strictly pulmonary, and few biochemical studies were undertaken, but the amount of serum globulin has been determined in 7 cases, and of these patients, 4 showed a definite increase in the serum globulin, the values ranging between 3 3 and 4 7 mg

of antibodies, but whether such a mechanism develops in this obscure new disease is highly questionable

In this connection the fact might be worth mentioning that the sedimentation rate was elevated in about half the cases of the delayed type of pulmonary disease in which the rate was determined In the acute form of the disease the sedimentation rate apparently is not increased

The phenomena which I have mentioned I consider secondary manifestations of the disease I agree absolutely with what Dr Howland said about the biochemical approach to this disease, we should not be satisfied with an attack on secondary problems, but should direct our investigations mainly toward a knowledge of the metabolism of beryllium in the body and of the effect of beryllium on cellular metabolism Before we can arrive at a reasonable understanding of the various phenomena of this disease, we must learn, for instance, what the state of beryllium is in the body fluids, when beryllium is present, does it occur only in the form of ions? Is the toxic agent possibly an inorganic compound or is it present in organic combination? I do not know the answers to these questions, and wonder whether anybody else does

Another question of considerable importance concerns the solubility of beryllium phosphate, as this property must determine the mechanism of the deposition of this compound in the bones Information on this point might give us a lead on the possibility of influencing the excretion of beryllium or its retention in the body by administering calcium

We must study the effects of beryllium not only on cells and cellular metabolism but also, particularly, on various enzymes Through such studies we may be able to arrive at an understanding of this puzzling disease and possibly devise a rational therapy

Further Discussion

DR KLEMPERER Dr Nickson, did you study patients actually suffering from the disease, which supposedly is due to beryllium, and if so, in any type of test were higher values found than those we have heard of as yet?

DR NICKSON. Unfortunately, we have had no opportunity to study the metabolic changes in human beings with clinical illness attributable to

exposed to beryllium but are not clinically ill with data on patients suffering from the chronic pulmonary disease. I am especially interested in Dr Nickson's studies of liver function because occasional laboratory data on patients with the chronic disease indicate some disturbance of liver function.

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of antibodies, but whether such a mechanism develops in this obscure new disease is highly questionable

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Further Discussion

DR KLEMPERER Dr Nickson, did you study patients actually suffering from the *disease, which supposedly is due to* beryllium, *and if so, in any* type of test were higher values found than those we have heard of as yet?

DR. NICKSON. Unfortunately, we have had no opportunity to study the metabolic changes in human beings with clinical illness attributable to

beryllium poisoning; we have made no tests with any subject suspected of such illness.

DR. KLEMPERER. Dr. Grier, have you observed any disturbance of liver function in cases of the acute disease?

DR. GRIER. As far as I know, no tests relating to hepatic function were made in such cases A few of the patients showed high levels of serum globulin

DR. KLEMPERER Dr. VanOrdstrand* stated, I think, that the results of all laboratory tests in the Ohio series of acute cases were negative. I wonder if any of the tests mentioned by Dr. Nickson were made in the Ohio series.

DR. VANORDSTRAND: No, none of those tests were made

DR SCORNAVACCHI: I should like someone to give us a list of the tests we should make so that in the future our data will have value for purposes of interpretation.

DR KLEMPERER: The fact that certain tests give abnormal results with some individuals exposed to beryllium does not necessarily mean that these individuals are the ones who will develop the disease later.

DR SCORNAVACCHI Perhaps my question was misunderstood I have one patient, hospitalized now, who I am sure has pneumonitis, whatever the cause. He has been exposed to beryllium Are there tests which I should make so that certain data will be available for future reference in the study of so-called beryllium pneumonitis?

DR. KLEMPERER We are interested in all liver function tests, for many metals have a predilection for the liver. We should like to know the serum globulin level It might be good to know the sedimentation rate, too.

DR. HOWLAND: I think we are in the position of not knowing what to study. For our program in connection with atomic energy, we selected certain liver function tests because we were familiar with the technics, and also because the associated pathology was thought to be connected with the liver to a certain degree. It is certainly impossible to know which of a group of tests to do As I have indicated, some tests give suggestive results, whereas others apparently are of no value In any case of the

* See Chapter 6 (Ed)

clinical illness, if you were in a position to "throw the book" at the patient, you could see what you had when you were through Perhaps it is only by such methods that ultimately we can pick out in a purely empirical way the tests which do have value

Whatever information you can get should be made known to others doing the same type of work, so that eventually we can sort out the specific tests which appear to yield valuable information, and can stop making the tests which are of no value Does that seem reasonable to you, Dr Klemperer?

DR KLEMPERER. *I certainly agree*

DR. WILSON Were any bromsulfalein tests done?

DR. KLEMPERER. From Dr Hardy I have knowledge of two bromsulfalein tests, in both of which the results were normal

DR WILSON In Salem we have started a series of tests in a few cases, and have observed no metabolic changes I should like to ask about the chronological relationship of increases in serum globulin to the onset of symptoms Were high globulin levels observed early at the onset of symptoms, or sometime afterward? Patients with the delayed disease often came to our attention not at the onset of symptoms, but weeks or even months later

DR KLEMPERER· Patients with the delayed disease have been studied only when they were severely ill This certainly is true of those studied at Saranac Lake, and the Massachusetts cases you know better than I do, Dr Wilson

DR. MARTLAND I think it is very important to note that tests of liver function have been made only in the last stages of the pulmonary disease, when the livers of the patients were enlarged by extreme passive congestion We have no information on liver function in the early stages of the disease

DR. KLEMPERER I believe the levels of serum globulin observed in this disease are higher than those observed in cardiac cirrhosis

DR. MARTLAND I still am under the impression that the extreme passive congestion of the liver observed in beryllium poisoning, often in association with extensive fibrosis, can explain some of the high values for serum globulin Furthermore, this granulomatous disease affecting the lungs

extensively, and the liver also in a few cases, is characterized by the presence of plasma cells, a fact which might explain the increased serum globulin. For this reason, I do not see how tests for such increases can be of any help toward early recognition of the disease.

MEMBER. One of the predominant symptoms of the disease is that all patients suffer a tremendous loss of weight. In my experience, serum globulin levels rise with loss of weight.

DR. KLEMPERER: The amount does not actually increase, the albumin decreases proportionally. In starvation you do not find serum globulin levels as high as those observed in some cases of the disease in question.

MEMBER: In certain experiments which my associates and I reported in the thirties, we did see a real increase in the serum globulin.

DR. KLEMPERER. But never an increase in the total proteins, as in cases of this new disease.

DR. MCCANN. I want to point out that epidemic hepatitis has become widespread, with many mild cases. In following up for a period of years patients who have had the condition, you will find that subclinical relapses, which may go on for five or six years or even longer, are characteristic of the disease. Studies of this kind were made in our clinic at the University of Rochester by Dr. Karnberg who is now in the Public Health Service. We followed up our medical students for a period of years. Hepatitis, of course, is going to come into this picture in this new disease and make the evaluating of changes in liver function almost impossible.

I suggest the thought that the increase in serum globulin observed in the beryllium cases may have a relation to the plasma cell reaction.

DR. VORWALD. An important question has been raised but not answered. I shall repeat it. what tests of liver function and renal function do the biochemists suggest as a starting point?

DR. KLEMPERER: I have mentioned a few liver function tests, but I do not say that these are the only ones that should be performed. The choice of procedures may depend on the facilities in a given laboratory. We do not really know whether some tests, which at present are considered liver function tests, measure liver function only. These tests can be made with single blood specimens, and do not require observation of the

patient for a long period The biochemist naturally wants tests such as those for galactose tolerance or glucose tolerance, which definitely give information on liver function.

I don't believe we should restrict ourselves to liver function tests The fact that the values found in some cases of the disease were abnormal has directed our attention toward the liver In a disease of undetermined nature, the greater the variety of tests that are made, the sooner something may turn up which will give us a lead

I want to emphasize the fact that we have data on only 40-odd cases of the chronic disease, and that we do not know whether the metabolic changes observed in some cases were due to the disease or were coincidental But the more clinical and laboratory data we gather of all kinds, the sooner we shall find an answer to the question about what tests we should make

DR NICKSON. I believe that our preliminary studies are of some interest because they raise the question of nonpulmonary systemic poisoning by beryllium Our organization is unable to continue these studies, but if some members of this symposium are stimulated to continue along the same lines, preferably with more heavily exposed subjects, our primary purpose in reporting our studies will have been achieved

Dr. Klemperer has circumvented a question to which we do not know the answer It may be that investigations with animals will help us to find the answer, but I gather that such investigations cannot be expected to give us the answer today or tomorrow, the work is going to take time In the meantime, we have on our hands a clinical problem which may be attacked empirically.

I should like to make a plea to the chemists for rapid, reliable, and simple methods of determining the amounts of beryllium and beryllium compounds in air Such methods are a sine qua non in the study of this disease

DR HOWLAND We cannot stress too strongly the singular fact that the hepatic and renal pathology may be manifestations secondary to the pulmonary manifestations Such pathology may occur in individuals prone to that type of reaction For this reason we need adequate controls such as Dr Vorwald suggested, that is, industrial workers who are exposed to beryllium but are resistant to pulmonary poisoning by this element

and have not developed the disease. In such individuals we might find some startling phenomena

DR VORWALD. At this time I want to announce that the following members of this symposium have been appointed to the nomenclature committee. Dr. Shipman, Dr. Howland, Dr. Sappington, Dr. Mayers, Dr. Cranch, Dr Vorwald, and Dr. Sanders. Dr. Sanders will act as chairman of the committee.

DR BRODKIN: May I inquire whether any of the members of the committee represent government agencies? I think the committee should include at least one member representing a state or federal agency

DR. VORWALD: Governmental agencies are represented by Dr. Howland and Dr. Mayers.

DR. BRODKIN: I should like to make a statement on the question of nomenclature. As has been pointed out, in 1945 the Cleveland group and the Massachusetts group called these diseases beryllium poisoning that is, beryllium pneumonitis appearing in workers exposed to beryllium In 1947 we are conducting a symposium in which more cases and more deaths are reported which confirm and support the papers published in 1945. On Monday, the first day of the symposium, the majority of the papers seemed to propose by very weighty evidence that beryllium was the cause of the disease. At the Tuesday session, though, we had again heard some very damaging evidence against beryllium Yet there were one or two speakers toward the close who went so far as to state that we shouldn't mention beryllium as the cause, and they were quite emphatic about it, because a bad reflection and unwarranted suspicion would be cast upon the beryllium industry.

I should like to point out that a similar attitude was directed toward the industries in which silica and asbestos were used Nevertheless, silicosis and asbestosis were officially classified as occupational diseases Now I would like to present this thought to the committee for their consideration. We may never scientifically reproduce the identical lesions in animals Leprosy is a case in point. Do we need more deaths and more respiratory cripples to convince us that beryllium compounds constitute an industrial hazard? It is extremely important to decide whether this is or is not an industrial hazard If it is, we must take steps to protect the employees in these industries and to compensate those who are disabled

in these industries, otherwise, industry will continue to be beset with one-hundred-thousand dollar civil suits instead of having them settled in the compensation courts where they belong By properly naming the beryllium compounds as an industrial hazard and naming the disease so that beryllium is recognized as a causative factor, we will take a definite step forward and this symposium will be fruitful of a definite contribution to industrial medicine.

DR. VORWALD. Dr. Sander, chairman of the nomenclature committee, *would like to make a few statements for that group. The Committee was* appointed to consider the terms that might best describe the pulmonary condition seen in individuals having contact with beryllium

DR. SANDER For the acute phase, your committee decided that *acute pneumonitis of beryllium workers* probably is the most descriptive term pathologically It certainly is a pneumonitis and it certainly is acute, and until we have definitely incriminated the beryllium radical it would not be correct, we feel, to call it *beryllium pneumonitis*. But we recognize that this condition occurs in beryllium workers and have, therefore, indicated that it is definitely an occupational disease

We are omitting the dermatitis cases in this title, but the dermatologists take care of that very well There are many external irritants to which they have attached names, and we shouldn't be concerned about that We are primarily interested in the pulmonary phases anyway

We also are disregarding the upper respiratory irritations by calling this pneumonitis, but those are only early manifestations of the resulting pneumonitis, nasopharyngitis, tracheobronchitis are just the forerunners In many cases, pneumonitis never develops The disabling condition, however, is the pneumonitis, which we have recognized. So much for the acute.

As for the chronic, the delayed changes, we have elected to call this *pulmonary granulomatosis of beryllium workers* The lesion which causes incapacitation is primarily pulmonary, even though there is evidence that there may be some systemic effect that is not definitely proved Until it is, we felt that we should call this a pulmonary disease, certainly, that is the incapacitating feature The pathologic lesion is a pure granuloma, the unit lesion, and we felt that it was more descriptive to use "granulomatosis" in the title, than to use the less definite "pneumonitis" This

also has the added advantage that, when one is discussing these things, each phase is clearly identified. No longer will there be need for the question. "Which pneumonitis do you mean, the acute or the chronic?" When we say granulomatosis, everyone will know that we are speaking of the chronic, delayed form.

DR. VORWALD. It seems to me that the terminology suggested will allow differentiation of the two types. It will not incriminate one special element, at least at the present time, until we are certain that that is the only factor. It allows us latitude to change as we see fit. I urge that the views of the committee be accepted The terminology, *acute pneumonitis of beryllium workers* and *pulmonary granulomatosis of beryllium workers*, is open for discussion from the floor.

DR. BRODKIN I should like to make a motion at this time that the committee be congratulated and thanked for its efforts.

(The motion was made and seconded.)

DR. HARDY. Dr. Vorwald, needless to say, you would expect to hear from me. I am not at all disappointed about the loss of my term specifically, but I do have two reservations One, I think it should be put to a vote of the Saranac Symposium. Two, I don't like "granulomatosis" because you can't make that diagnosis until your patient is dead. That is a pathologic diagnosis All the rest is fine, but I think we ought to put the thing to a vote.

DR VORWALD In view of current knowledge concerning the delayed form of the disease, the committee felt that specific reference to the pulmonary condition could best be made on the basis of actual pathology which in final analysis accounts for the most prominent clinical manifestations of the disease. The pathologic lesion in the lung is a chronic form of inflammation not unlike a granuloma It is seen roentgenographically and is accompanied by respiratory difficulties The term suggested, *pulmonary granulomatosis in beryllium workers*, differentiates the condition from the acute forms of the disease The term permits a latitude for change should subsequent events justify it.

(A motion was made and seconded to vote on the adoption of the terms suggested by the nomenclature committee.)

DR BRODKIN. I question the propriety of putting this medical question to a vote before this entire body, which is composed of lay and medical

people It is my belief that it should be voted upon by the medical members of the symposium if we are to register our vote.

DR VORWALD You have heard Dr. Hardy's suggestion A motion has been made and seconded. You have the comment by Dr Brodkin. Do you wish to bring the motion that has been made and seconded to a conclusion by calling for a vote, or do you wish to vote that the motion be delayed?

It is obvious that you wish to vote on the terminology at this time. A motion has been made and seconded What is your opinion by a show of hands—do you accept the terminology as identified by the committee? Those not in favor will signify by raising their hands .

It is quite evident that you approve of the terminology which identifies the acute phase of the disease as *acute pneumonitis of beryllium workers* and the chronic or delayed phase as *pulmonary granulomatosis of beryllium workers.*

Pathology of Acute Experimental Beryllium Poisoning: Changes Resulting in Venous Blood from the Intravenous Administration of Beryllium Sulfate

JAMES K. SCOTT, M.D.*

Soluble beryllium compounds act as irritants when they come in contact with tissues, for example, when they are injected subcutaneously or intraperitoneally, or when they are inhaled. For this reason one must distinguish the local irritation from the general effects on organs distant from the site of administration The gross and microscopic observations described in the following pages were mainly the results of two studies In the first study, animals were exposed to an atmosphere containing beryllium sulfate dust During this experiment the principal lesions occurred in the lungs, skin, and eyes The second study consisted of a series of experiments in which beryllium sulfate was administered intravenously, for the purpose of defining the general effects of beryllium poisoning. Beryllium sulfate was used in these experiments because it can be obtained in fairly pure form, and because it was not believed that the sulfate ion would alter or mask the action of the beryllium When soluble beryllium compounds other than beryllium sulfate were administered intravenously to animals, the lesions of the liver, kidneys, and hemopoietic system were the same as those resulting from beryllium sulfate. Rats were used exclusively in the experiments described here, in which the beryllium sulfate was administered intravenously Guinea pigs and rabbits were studied also, however, and the lesions produced in these species were found to be much the same as those in the rat.

* Head, Pathology Section, Division of Pharmacology, Atomic Energy Project, University of Rochester, Rochester, New York

Local Effects of Beryllium Poisoning

The inhalation experiment was carried out as follows Rats, mice, guinea pigs, hamsters, rabbits, and dogs were exposed for six hours daily for a period of 11 days to an atmosphere containing beryllium sulfate dust. The mean concentration of the dust was 88 mg. per cubic

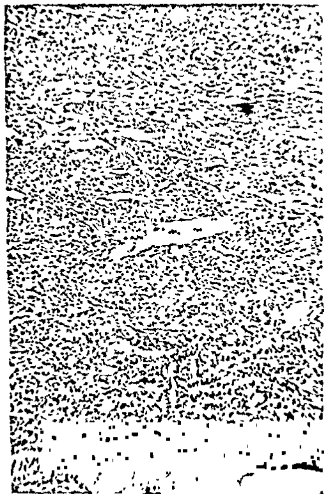


FIG. 78 Section of eye tissue, ×100, from a guinea pig killed after 11 days of exposure to an atmosphere containing 88 mg of beryllium sulfate dust to each cubic meter of air A corneal ulcer and evidence of keratitis are shown (bottom of illustration)

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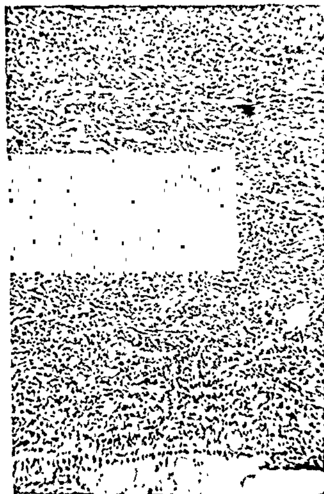


Fig. 76 Section of eye tissue, ×100, from a guinea pig killed after 11 days of exposure to an atmosphere containing 88 mg. of beryllium sulfate dust to each cubic meter of air. A corneal ulcer and evidence of keratitis are shown (bottom of illustration)

meter of air, and the mean size of the particles was 4.5 microns The animals which died during the experiment were autopsied, and those which survived until the end of the experiment were then killed and autopsied

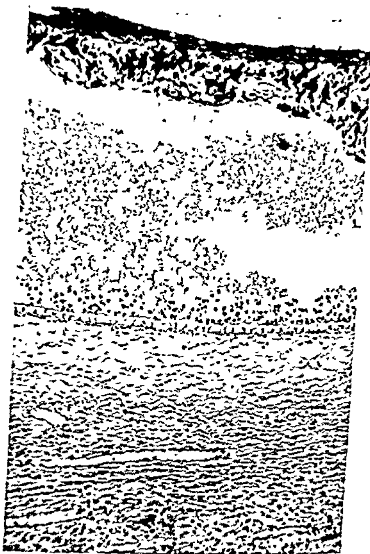


Fig 79. Same section in fig 78, ×100, showing the purulent exudate in the anterior chamber of the eye (upper half of illustration).

The gross lesions seen in the lungs at autopsy included consolidation, hemorrhage, and edema, of varying degrees Foci of emphysema alter-



Fig. 80 Lung tissue from a guinea pig exposed in the same manner as the animal which provided the specimens shown in figs 78 and 79 This section shows minimal evidence of the pulmonary disease observed in guinea pigs in inhalation experiments with beryllium sulfate

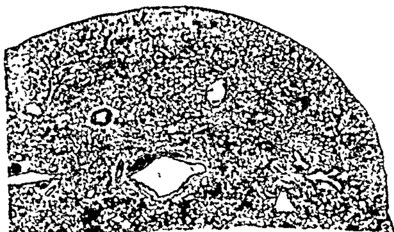


Fig. 81 Lung tissue from a rabbit exposed to beryllium sulfate in the same manner as the guinea pig of fig 80 The pulmonary pathology was found to be more diffuse and more severe in the rabbit than in the guinea pig

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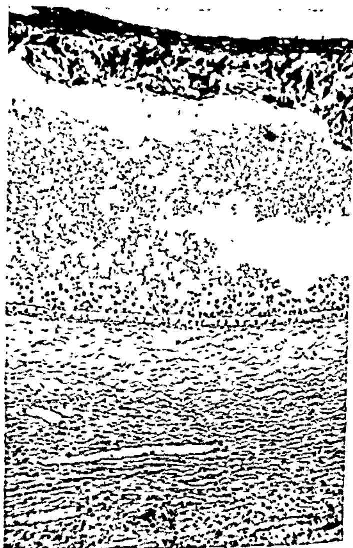


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Fig 81 Lung tissue from a rabbit exposed to beryllium sulfate in the same manner as the guinea pig of fig 80. The pulmonary pathology was found to be more diffuse and more severe in the rabbit than in the guinea pig

nated with areas of atelectasis and consolidation. On section some lungs were found to contain tiny purulent foci The extent of disease varied considerably among the different species; the rabbits, rats, and mice exhibited extensive pulmonary disease, whereas the guinea pigs and hamsters showed a minimum of lung lesions.



FIG 82. Tissue specimen, ×180, showing the bronchial and alveolar exudate in a guinea pig which for 11 days breathed an atmosphere containing 88 mg of beryllium sulfate in each cubic meter of air

The eyes of the guinea pigs and dogs developed conjunctivitis during the course of exposure, and in some animals corneal opacity was observed The dogs developed ulcers of the nose and feet, with abundant granulation tissue appearing about the ulcers.

On microscopic examination the diseased eyes showed acute conjunctivitis and keratitis. In some animals corneal ulcers were seen in which the cornea was replaced by organizing granulation tissue, in such an

eye a purulent exudate was observed in the anterior chamber (figs 78 and 79) The skin lesions of the dog consisted of a superficial ulceration of the epithelium, the base of the ulcer consisting of granulation tissue



FIG 83 Tissue specimen, ×120, showing the ulceration and hyperplasia of the bronchial epithelium in a rat exposed to beryllium sulfate in air in the manner previously described

The pulmonary lesions resulting from exposure to beryllium sulfate dust were fundamentally much the same in all the species examined, in its extent and degree of severity, however, the pulmonary disease varied widely among the different species (figs 80 and 81) Intra-alveolar edema of varying degree, accompanied by some interstitial edema and by

thickening of the alveolar walls, *was the earliest* disturbance observed *in the lungs* Collars of fluid were seen about the larger arteries. This phenomenon was followed *by an exudation of* neutrophils and phagocytic cells into the terminal bronchi and the surrounding *alveolar sacs* Many *of the* cells *of the* exudate disintegrated. This disintegration

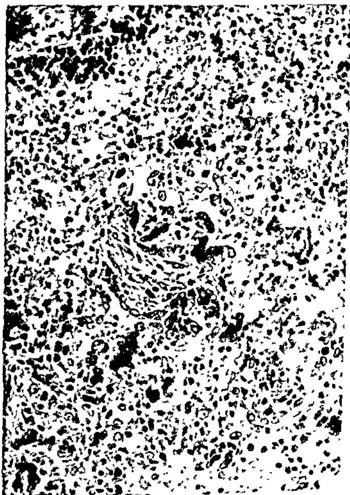


Fig 84 Tissue specimen, ×200, showing the organization of the bronchial exudate in a rat exposed to beryllium sulfate in air for 11 days.

resulted in a fairly characteristic tissue reaction. In the terminal bronchi and some of the surrounding alveoli a dense, somewhat granular, deeply eosinophilic coagulum occurred which contained much nuclear debris

(fig 82). Ulceration of the smaller bronchi, of varying degree, apparently was followed by an exuberant overgrowth of the bronchial epithelium, which sometimes formed adenomatoid nests. In the more diseased areas the bronchial epithelium extended into the alveoli, lining the alveoli with a layer of cuboidal epithelium (fig. 83). Little organization of the exudate and little fibrosis were observed, probably because the experiment was of such short duration. Occasionally, however, fibroblasts were observed growing into the exudate (fig. 84) In many lungs small, irregular structures of a homogeneous blue color were seen, these bodies, the composition and significance of which are not known, were observed in many animals receiving different beryllium compounds by different routes

General Effects of Beryllium Poisoning

Animals receiving soluble beryllium compounds developed lesions in organs and tissues distant from the site of administration Such lesions most often were observed to follow intravenous or intraperitoneal administration of the beryllium compounds, but occurred also in some species after ingestion or inhalation of the compounds. In the inhalation experiment reported here, the mice showed varying degrees of liver necrosis, and the rabbits and rats showed necrosis of the renal tubular epithelium. To make possible more precise characterization of these lesions, beryllium sulfate in different doses was administered intravenously to rats, the animals being killed at intervals (usually of one day) thereafter, and the organs examined

Inasmuch as the severity and even the development of lesions depends to some extent on the dosage, some statement should be made concerning the toxicity of beryllium sulphate for rats. The intravenous LD_{50} of hydrated beryllium sulfate ($BeSO_4\ 4H_2O$) is approximately 7.2 mg per kilogram for white female rats of the strain used in this laboratory and weighing between 175 and 200 gm An occasional rat receiving 6 mg. per kilogram has died and an occasional rat receiving 8 mg. per kilogram has survived.

Gross Changes Observed in Rats Receiving Beryllium Sulphate Intravenously

When rats have been given large doses of beryllium sulphate intravenously (15 mg/kg or more) they usually die three or four days later An exudation of fluid into the serous cavities and petechiae has been observed in such animals. When smaller doses, around the LD_{50},

were given this was not usually seen The spleen was enlarged, two or three times, the capsule was tense, and it had a deep purple color. In animals dying three or more days after injection, icterus was always observed.



Fig 85 Hepatic tissue, ×120, from a rat killed 5 days after an intraperitoneal injection of 20 mg of beryllium sulfate per kilogram of body weight This specimen illustrates the extensive necrosis which left only a layer or two of viable cells, seen in portal areas

Microscopic Findings

Liver necrosis of the liver cells was uniformly observed when beryllium sulfate was administered intravenously in doses of 6 mg/kg or

more The extent of necrosis seemed to be roughly proportional to dosage, thus, the livers of animals receiving 6 mg /kg intravenously showed only small focal necrosis whereas those receiving 7 or more mg /kg usually showed widespread necrosis, sometimes so extensive



FIG 86 Hepatic tissue, ×400, from a rat killed 3 days after an intravenous injection of 6 mg of beryllium sulfate per kilogram of body weight Small midzonal necrotic areas, the earliest hepatic lesions observed in experiments with this dosage, are shown

that only a layer or two of viable liver cells remained about the portal areas (fig 85) The smallest lesion consisted of a focal area containing a few necrotic cells in the midzone or the paracentral area of the liver

lobule (fig. 86). The liver cells became swollen, assumed a deep homogeneous eosin stain, the nuclei became pyknotic and later disappeared completely This liver necrosis did not become evident until the third day after administration of the beryllium sulfate During the following



Fig 87 Hepatic tissue from a rat killed 4 days after an intravenous injection of 6 mg. of beryllium sulfate per kilogram of body weight. This specimen, ×120, shows liquefaction and absorption of liver cells

three days (fourth to sixth days) the necrotic cells were gradually lysed and disappeared (fig 87). After disappearance of the cells an area re-

remained which consisted of the connective tissue framework of the liver and the sinuses A few mononuclear cells and occasional polymorphonuclears were seen in these foci The reticulum and connective tissue was unaffected by the beryllium (fig 88) On the sixth or seventh days

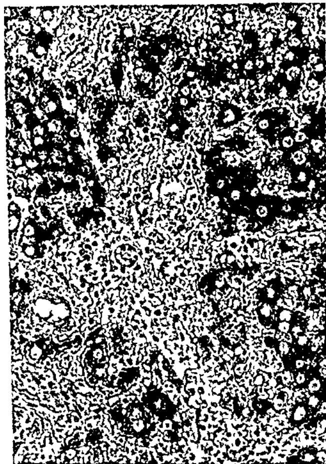


FIG 88 Hepatic tissue, ×100, from a rat killed 8 days after an injection of 8 mg of beryllium sulfate per kilogram of body weight This specimen, stained with Wilder reticulum stain, shows the preservation of the reticulum.

regeneration began as evidenced by an increased number of mitoses. The speed with which regeneration proceeded depended on the extent

of the lesions but in all cases it was completed by the end of two weeks, at which time the livers were microscopically normal. There was no evidence that growth of connective tissue was stimulated, and no scar has ever been observed after a single intravenous injection. Considerable disturbance of the fat of the hepatic cells as indicated by Sudan IV stains

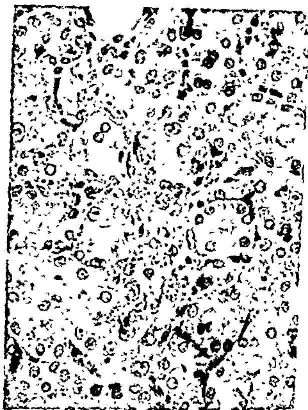


FIG. 89 Section of the inner third of the renal cortex, ×400, from a rat killed 6 days after an intravenous injection of 5 mg of beryllium sulfate per kilogram of body weight Note the isolated cells with pyknotic nuclei

was observed. The necrotic cells contained a small amount of finely divided fat which took brownish stains The viable and apparently normal cells which surrounded the necrotic foci contained large droplets of fat taking the usual deep orange stain. The fat was observed in these cells after the necrotic cells had disappeared and was present in the regenerating cells which replaced the necrotic cells. Two weeks after

the beryllium sulfate was administered no stainable fat was found in the liver.

Kidney changes. renal changes have been observed in animals receiving beryllium sulfate intravenously, intraperitoneally, and by inhalation The lesions consisted of necrosis of tubular epithelial cells, the process

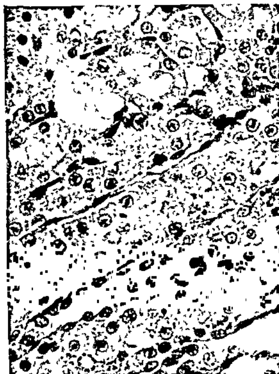


FIG. 90 Renal tissue from a rabbit killed after 11 days of exposure to an atmosphere containing 88 mg of beryllium sulfate dust per cubic meter of air Necrosis and desquamation of tubular epithelial cells are shown

involving mainly the distal third of the proximal convoluted tubule. This necrosis was never widespread and usually only a few cells in each field exhibited degeneration changes The first changes observed occurred three days after administration of the beryllium sulfate intravenously and consisted of a change from the finely granular appearance of the

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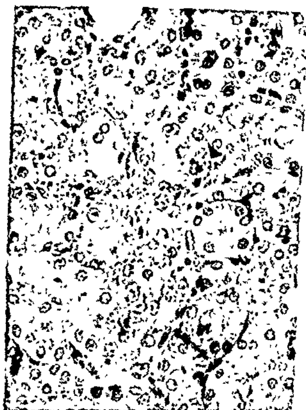


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Spleen: microscopic changes were observed in the spleen only when doses of the L.D.$_{50}$ or greater were used. The principal change seen was a marked congestion of the sinusoids in which large amounts of nuclear debris were found. Active lymphoid nodules disappeared. The lymphocytes showed a clumping of the chromatin at the periphery of the nucleus, this was probably followed by karyorrhexis and the disintegrated nuclei supplied some of the nuclear debris found in the pulp. This resulted in a marked decrease in the number of nucleated cells in the spleen

The *bone marrow* and the *lymph nodes* showed changes similar to those of the spleen but much less marked. The bone marrow also exhibited a granulocytic hyperplasia.

Changes Resulting in Venous Blood from Intravenous Administration of Beryllium Sulphate

The interpretation of changes in the blood elements after administration of beryllium sulfate by routes other than the intravenous is difficult or impossible because beryllium acts locally as an irritant. When administered intravenously, there is no local inflammatory reaction and any changes occurring must result from generalized action of the compound which, at least for a period of time, is carried to most of the tissues of the body.

The procedure in this experiment was simply to follow the blood counts, usually daily, for two weeks or longer after a single intravenous injection of beryllium sulfate. The doses of beryllium sulfate tetrahydrate were 7.2, 5.0, 3.0, and 1.5 mg./kg. Eight rats were used at each level. Figures 91, 92, and 93, indicate the average counts of the different elements from the 8 animals at each level

The red counts at doses of 7 2 and 5 0 mg /kg showed a slow elevation during the first three or four days after administration of the beryllium sulfate, this was followed by a precipitous drop in count which returned to normal about two weeks after the injection On about the fourth day after the administration, there was a rapid increase in the percentage of

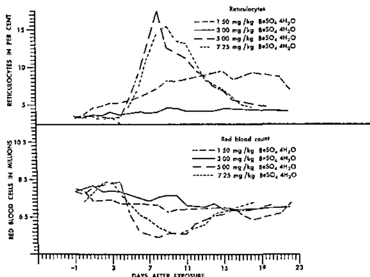


FIG 91 Average daily changes in the reticulocyte and erythrocyte counts of rats after the intravenous injection of hydrated beryllium sulfate Averages are shown for four groups (8 rats per group) receiving different dosages

reticulocytes and nucleated red cells This anemia and reticulocyte response failed to develop in animals receiving less than 5 mg /kg (fig 91)

No definite statement can be made concerning the cause of this anemia However, it would appear that during the period of three to four days following administration of the compound there occurred concomitantly a hemoconcentration and an intravascular lysis of red cells, this was followed by a return of the plasma volume to somewhere near normal The hemolysis with resulting anemia must have begun at the time of administration of the compound since the reticulocyte response occurred on the fourth day

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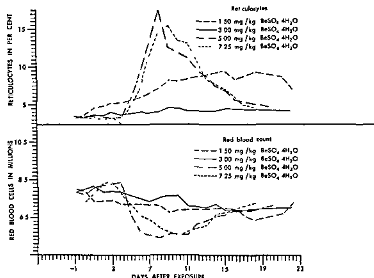


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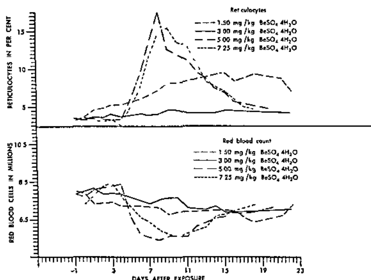


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The procedure in this experiment was simply to follow the blood counts, usually daily, for two weeks or longer after a single intravenous injection of beryllium sulfate The doses of beryllium sulfate tetrahydrate were 7.2, 5.0, 3.0, and 1.5 mg./kg. Eight rats were used at each level. Figures 91, 92, and 93, indicate the average counts of the different elements from the 8 animals at each level

The red counts at doses of 7.2 and 5.0 mg./kg. showed a slow elevation during the first three or four days after administration of the beryllium sulfate; this was followed by a precipitous drop in count which returned to normal about two weeks after the injection. On about the fourth day after the administration, there was a rapid increase in the percentage of

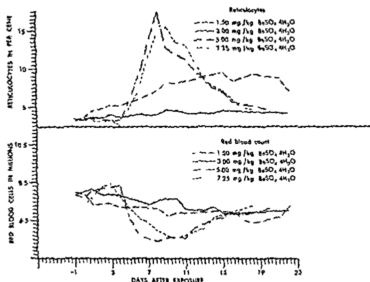


FIG. 91. Average daily changes in the reticulocyte and erythrocyte counts of rats after the intravenous injection of hydrated beryllium sulfate. Averages are shown for four groups (8 rats per group) receiving different dosages.

reticulocytes and nucleated red cells. This anemia and reticulocyte response failed to develop in animals receiving less than 5 mg./kg. (fig. 91).

No definite statement can be made concerning the cause of this anemia. However, it would appear that during the period of three to four days following administration of the compound there occurred concomitantly a hemoconcentration and an intravascular lysis of red cells; this was followed by a return of the plasma volume to somewhere near normal. The hemolysis with resulting anemia must have begun at the time of administration of the compound since the reticulocyte response occurred on the fourth day.

There was a marked increase in the total white cell count, reaching a peak on the second to fifth day after administration of the compound. This leukocytosis was a result of an absolute increase of neutrophils. The number of neutrophils increased from around a normal of 4000 per cubic mm. to around 22,000 per cubic mm. The count then gradually decreased

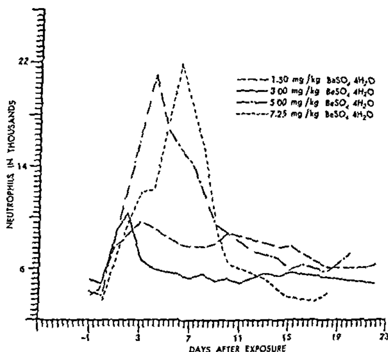


FIG. 92 Average daily absolute increases or decreases in neutrophils in rats after the intravenous injection of beryllium sulfate. Each line shows the average changes for a group of 8 rats receiving a particular dosage.

and on the ninth or tenth days approached normal. This leukocytosis occurred in all animals at the levels of 7.2, 5.0, and 3.0 mg./kg., at 1.5 mg./kg. only about one-half of the animals showed this change (fig. 92).

The most interesting change occurred in the platelets. At 7.2 mg./kg a sharp drop in the number of platelets occurred on the third day and the lowest point was reached on the sixth, following which there was a gradual increase which reached normal about two weeks after administration of the beryllium sulfate. When doses of 5.0, 3.0, and 1.5 mg. were used, the platelet response was exactly the opposite. At 5.0 mg./kg

there was a slight depression followed by a rise on the fourth day which reached a peak of almost three times the control level on about the seventh day, after this, the counts gradually decreased, approaching control levels after two weeks At levels of 3 0 and 1 5 mg /kg , no initial depression of the count occurred, and the counts began increasing twenty-

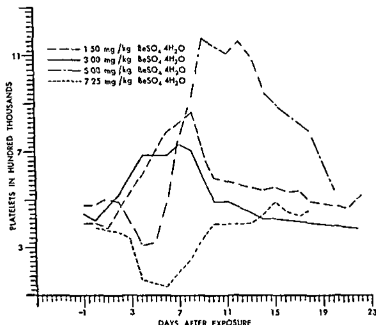


FIG 93 Average daily changes in the platelet count of rats after the intravenous injection of beryllium sulfate Each group of 8 rats received a different dosage

four hours after administration of the beryllium sulfate and reached the peak on the 9th and 10th days (fig. 93).

Discussion

PHILIP C PRATT, M D.*

This is a very interesting paper, and I think it shows careful observation and thorough study of the animals used in this experiment I was

* Pathologist, The Saranac Laboratory, Saranac Lake, New York

interested to note in the intravenous phase of the experiment the fairly wide variation in response to the lethal doses in that range, and in view of that, I was interested in the apparent constancy of the reaction in the kidneys to those doses.

In the paper, as I read it, Dr. Scott pointed out that the lesions were constantly seen in the kidneys of the animals given 6 mg., but in only an occasional animal given 5 mg. I'd like to ask Dr. Scott if he has an explanation for this.

Concerning the dust concentration in the experiment, we measure ours in milligrams per cubic foot of air and by this measurement Dr. Scott's concentration comes out to about 3 mg. per cubic foot. In our experiments we have planned to put into suspension about 0 3 to 0 4 mg. per cubic foot, about one-tenth of what Dr Scott was using Probably this concentration which we intend to maintain is pretty high, so I think he is correct in emphasizing that he is using a rather inordinately high concentration

He didn't say anything about the range of particle size of the dust, and there probably was a tendency toward clumping, which might produce excessive localization in the bronchioles.

We have done an inhalation experiment with beryllium sulfate. We used it dissolved and sprayed it into the atmosphere the animals were *breathing. It is probably not as satisfactory a method as Dr. Scott's. In* our experiments we produced lesions like those he has found, there were *macrophages in the alveoli, but the cells did not contain dust* particles because we were not putting dust particles in There was also slight *necrosis scattered in the liver, the material apparently* being absorbed and acting essentially the way it does when injected intravenously

The photomicrographs that Dr Scott showed of his results with inhalation certainly look very, very much like the human lesion to me I can't specifically say that I have seen it in the terminal bronchiole, but I have seen it in the alveoli, and I believe Dr Scott has come very close to, if he hasn't actually reproduced, the acute human lesion. However, the lesion resembles in no way the lesion of the delayed form of the disease.

As far as Dr. Scott's studies on the blood are concerned, I think his theory is very reasonable I wouldn't have any idea what to think of the platelet changes myself. However, the changes in blood, it might be

pointed out, are not comparable to those in the human cases, which depend on the interference with pulmonary function

We have made a few observations of the changes in the blood in animals following intravenous injections In the injection of zinc beryllium silicate in repeated small doses, we have found, after two months, that the total blood count is normal, but strikingly enough, that there is a reversal of the lymphocyte-polymorph ratio I wouldn't try to draw any conclusions from that, either.

Further Discussion

DR SCOTT: This inhalation experiment will be described in more detail later In answer to the question about the kidney lesions occurring at a lower dosage than the liver lesion the liver lesions were found constantly at 6 mg/kg and only occasionally at 5 mg/kg, whereas the kidney lesions were found at 5 mg/kg I'm sure a certain amount of beryllium must be excreted through the kidney, and this may produce lesions much as in uranium poisoning

DR PRATT. I was interested in the wider variation in dosage which produced the lesions in the kidney.

DR NEUMAN From looking over the information available on the chemistry of beryllium, it's fairly evident that beryllium does not exist as a divalent ion at physiologic *p*H It forms beryllium hydroxide or hydrate in solutions above *p*H 5 0 unless certain complexing agents are present Since the hydrate of beryllium has a very limited solubility, it is probable that only the low dosages of beryllium remain soluble in plasma, thereby filtering through the glomerulus and damaging the kidney. Higher doses may exceed the solubility of beryllium in plasma, thereby resulting in particulate material which could be taken up by the reticulo-endothelial system, and deposited in the liver. This is entirely theory, *without any experimental evidence*, but it offers a rational explanation of the fact that low doses cause kidney damage, high doses, kidney and liver damage.

DR KLEMPLRER Are solubility data on $Be(OH)_2$ available?

DR. NEUMAN We have had several problems with the solubility of $Be(OH)_2$ We are working on it at present

DR. KLEMPERER: What do you base the theory on, that the beryllium ion could not exist at physiologic pH?

DR. NEUMAN. I'm sure you'll find data bearing on that point in the literature

MEMBER: I was wondering, what was the pH of the solution? What was the concentration of the beryllium sulfate in the solution used for injection and was there any effect on the site of the injection? How many rats were used in each group?

DR SCOTT: The pH was around three. The injections were made as slowly as possible. No solution was lost in the tissues.

MEMBER. Was there any clot around the site of the injection?

DR. SCOTT No, there was none. I have done a number of intravenous injections of beryllium sulfate on the same rat, using the same vein and have never observed a thrombus. In establishing the LD_{50}, 20 rats were used in each group.

MEMBER: The reason I asked these questions was that if you take salts of beryllium, you would have some effect at the site of the injection because of increased concentration I was wondering if you would have complicated effects

DR SCOTT: I haven't been able to show any.

DR BARKULIS. Were any specific control animals given sulfates other than beryllium?

DR. SCOTT Sulfate ions of the concentration and pH of the beryllium sulfate used in these experiments had no recognizable effect on the animals.

DR. DUTRA. Did these animals die that were exposed to the dust, or were they killed?

DR SCOTT. That will be brought out later Only the mice died, the others were killed at the end of the experiment.

DR DUTRA. Fourteen days after the end of the exposure?

DR SCOTT: The exposure lasted 14 days, they were killed on the evening they were taken out of the chamber.

CHAPTER 18

Preliminary Data on Rat Feeding with Beryllium

ELLIOTT A. MAYNARD,* WILLIAM L DOWNS,
AND HAROLD C. HODGE, PH.D †

In order to obtain some preliminary information on the effects of the ingestion of beryllium, albino rats of the Wistar strain, raised in our own colony, were fed various dietary levels of beryllium metal and of certain beryllium salts Because of the limited amount of available laboratory space where proper precautions could be taken to prevent exposure to beryllium of other experimental animals, as well as of personnel, only two rats per dietary group were fed at one time

Hydrated Beryllium Sulfate

Effect on Growth Two male rats (28 days old, average body weight 62 gm) were fed a diet containing 5 per cent beryllium sulfate for a period of 172 days, at which time one of the animals died and the other was killed for histopathologic study As may be seen in the accompanying growth curves (fig 94) a marked depression of growth was noticeable from the very beginning of the experiment, at the termination of the experiment the average body weight of the rats on the special diet was 306 gm less than that of the control rats.

In a repeat experiment with 2 male weanling rats (age 28 days, average body weight 62 gm), one animal died at the end of 71 days on the diet and the second one was killed At that time the average weight of the experimental rats was 234 gm. less than that of the control rats (fig 94)

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† Head, Division of Pharmacology, Atomic Energy Project, University of Rochester, Professor of Pharmacology, School of Medicine and Dentistry, University of Rochester

Effect on Food Consumption: Records of food consumption were kept for 2 male weanling rats (28 days old) on a diet containing 5 0 per cent beryllium sulfate for a period of 180 days. The average amount of food ingested by these rats daily was about 7 gm., as compared with about 15 gm for the control rats. Figure 95 shows growth curves and food consumption curves for these animals

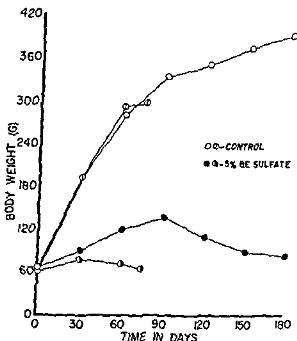


FIG 94 Growth curves of rats (2 males per group) fed a diet containing 5 per cent hydrated beryllium sulfate.

Paired Feeding. In order to determine whether the depression in growth of the rats fed a diet containing 5 0 per cent beryllium sulfate was due entirely to reduced food intake, 2 control rats were fed each day an amount of stock diet equal in weight to the experimental (5 per cent beryllium sulfate) diet consumed the day previous by their littermate brothers This regimen was continued for a period of sixty-eight days At that time the rats receiving 5 0 per cent beryllium sulfate in the diet had average body weights of 91 gm as compared with 133 gm for the controls, a difference of 42 gm. Growth curves are shown in fig 96. Radiographs of the experimental rats showed a rickets-like con-

dition of the tibial head during the latter part of the experiment This condition was principally indicated by an enlargement of the metaphyseal space (fig 97). This would seem to indicate a definite toxic effect following the ingestion of 5 0 per cent beryllium sulfate by rats.

Recovery After Ingestion of Beryllium Sulfate In order to determine the extent of recovery possible following the ingestion of beryllium sul-

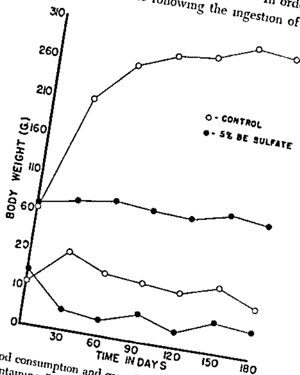


FIG 95 Food consumption and growth curves of 2 male rats fed a diet containing 5 per cent hydrated beryllium sulfate

ate, the two rats from the above experiment were returned to a stock et at the end of sixty-eight days Radiographs (fig 98) made 144 hours ter the rats were returned to stock diet showed good healing of the ial head Figure 96 shows that after fifty-two days on a stock diet the rage body weight of the experimental rats was 47 gm less than that he controls Radiographs taken somewhat later (fig 99) showed an rely new development in the proximal portion of the tibia, in the form well-defined radiolucent area A radiograph of an entire rat (fig 100)

shows this peculiar condition in the distal end of each femur as well as in the proximal ends of the tibias Figure 101 shows growth curves for two other rats that were returned to a stock diet after receiving 5 0 per cent beryllium sulfate for a period of 40 days At the end of 100 days on the stock diet these 2 rats had an average body weight 63 gm less than that of the controls.

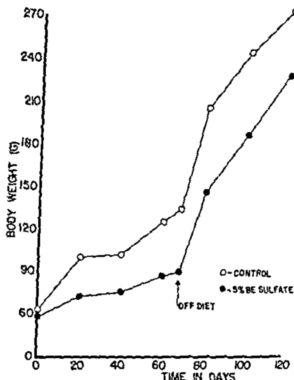


FIG 96 Growth curves of 2 male rats fed a diet containing 5 per cent beryllium sulfate for 68 days, and then a stock diet for 52 days.

Effect of Single Dose (Twenty-four Hr) Feeding of 5.0 Per Cent Beryllium Sulfate. Figure 102 shows there was no noticeable effect on food consumption or growth of two weanling rats which were fed 5 0 per cent beryllium sulfate in the diet for a twenty-four hour period

Age as a Factor in the Toxicity of Beryllium Sulfate in Rats Two male rats (age 173 days) and two male rats (age 81 days) were fed a diet containing 5 0 per cent beryllium sulfate Figure 103 shows growth curves for these animals At the end of sixty days one of the older rats



FIG. 97 On the left is a radiograph of the tibial head of a control rat, on the right, a radiograph showing the tibial head of a rat fed for 68 days on a diet containing 5 per cent beryllium sulfate Note the enlargement of the metaphyseal space



FIG 98 On the left is shown the tibial head of a control rat, on the right, the tibial head of a rat 6 days after the animal, fed for 68 days a diet containing 5 per cent beryllium sulfate, was returned to a stock diet Note the prompt healing



FIG 99 On the left is shown the tibial head of a control rat, on the right, the tibial head of a rat 76 days after the animal, fed for 68 days a diet containing 5 per cent beryllium sulfate, was returned to a stock diet The proximal section of the tibia shows a radiolucent area

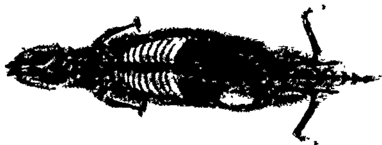


FIG 100. Skeleton of a rat fed a diet containing 5 per cent beryllium sulfate for 68 days, and then returned to a stock diet This radiograph was made 122 days after the return to ordinary food Note the radiolucent areas in the distal ends of the femurs as well as the proximal sections of the tibias.

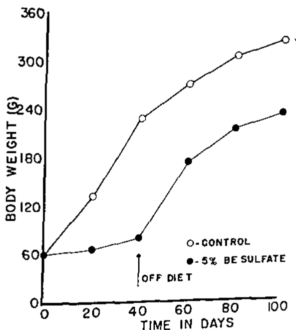


FIG 101 Growth curves of 2 male rats fed a diet containing 5 per cent beryllium sulfate for 40 days, and then a stock diet for 60 days

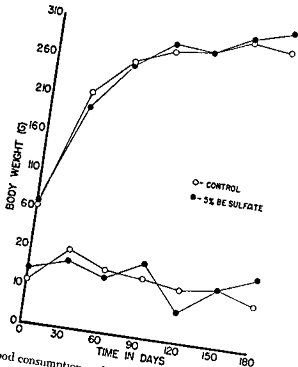


Fig 102 Food consumption and growth curves of 2 male rats fed a diet containing 5 per cent beryllium sulfate for 24 hours

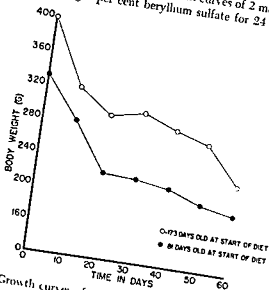


Fig 103 Growth curves of mature male rats (2 per group) fed a diet containing 5 per cent beryllium sulfate

died. At that time the average body weight of the two animals was 222 gm as compared with an average initial weight of 399 gm; an average loss of 177 gm. In the sixty-day period the eighty-one-day-old rats decreased from an average initial body weight of 330 gm. to 175 gm; a loss of 155 gm. Thus it seems that beryllium sulfate is more toxic to older rats than to weanlings (4 weeks old).

TABLE XXX RATS OF VARIOUS AGES (2 PER GROUP) FED 5.0% BERYLLIUM SULFATE IN THE DIET

Average Starting Age	Average Body Weight	Average Weight Change	Mortality
28 days	62 gm.	+ 20 gm	172 days, sacrificed
28	62	+ 8	71 days, sacrificed
81	330	−181	94 days, alive
173	399	−177	60 days, alive

Beryllium Carbonate

5.0% Dietary Level

Effect on Growth. Two weanling male rats (age 30 days; average body weight 64 gm.) were fed 5.0 per cent beryllium carbonate in the diet. These animals lost weight steadily and died in 39 and 59 days (fig. 104). Radiographs (fig. 105) of the tibial head showed the same rickets-like condition in these rats as was reported above for rats fed 5.0 per cent beryllium sulfate.

Age as a Factor in the Toxicity of Beryllium Carbonate in Rats: Two male rats (180 gm. average initial weight, age 49 days) were fed a diet containing 5.0 per cent beryllium carbonate. Growth curves (fig. 106) show that these rats lost weight steadily and died after nineteen and thirty-three days. In these rats again, the rickets-like condition of the tibial head appeared. This may be seen in a radiograph (fig. 107) taken twenty-seven days after the start of the experiment. This rat died in thirty-three days. The two control rats were then (age 99 days) placed on a diet containing 5.0 per cent beryllium carbonate for a period of sixty-five days during which time they maintained their weight (fig. 106). In table XXXI it may be seen that in direct contrast to the effect of

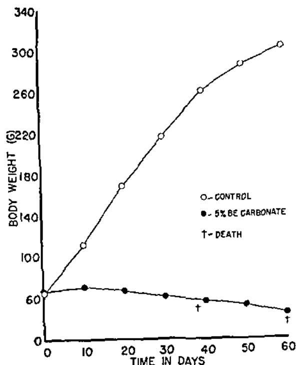


Fig 104 Growth curves of 2 male rats fed a diet containing 5 per cent beryllium carbonate

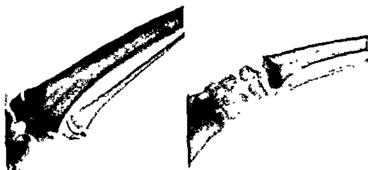


Fig 105 On the left is shown the tibial head of a control rat, on the right, the tibial head of a weanling rat after 42 days on a diet containing 5 per cent beryllium carbonate

TABLE XXXI RATS OF VARIOUS AGES (2 PER GROUP) FED 5.0% BERYLLIUM CARBONATE IN THE DIET

Average Starting Age	*Average Body Weight*	*Average Weight Change*	*Mortality*
30 days	64 gm	−10 gm.	39 days, 59 days
49	130	−50	19 days, 33 days
99	248	0	none/65 days

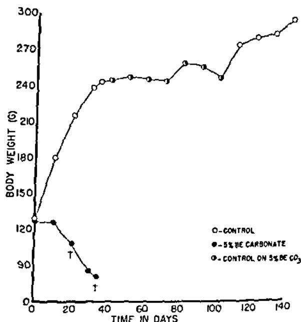


FIG 106 Growth curves of rats (2 males per group) fed a diet containing 5 per cent beryllium carbonate.

beryllium sulfate as given in table XXX, mature rats are somewhat more resistant to beryllium carbonate in the diet than are weanlings.

Recovery Following Ingestion of Beryllium Carbonate. The two mature rats (age 99 days) were returned to a stock diet after seventy days on a diet containing 5 0 per cent beryllium carbonate These rats (now one-hundred-and-sixty-four days old) immediately made a spurt in growth and at the end of forty-eight days had made an average weight gain of 40 gm. and appeared to be normal animals (fig. 106).



Fig 107 On the left is shown the tibial head of a control rat, on the right, the tibial head of a mature rat after 27 days on a diet containing 5 per cent beryllium carbonate

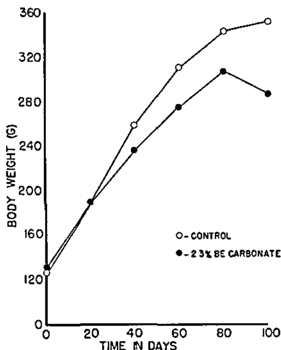


Fig 108 Growth curves of 2 male rats fed a diet containing 2 3 per cent beryllium carbonate



FIG 109 On the left is shown the tibial head of a control rat, on the right, the tibial head of a rat after 56 days on a diet containing 2 3 per cent beryllium carbonate

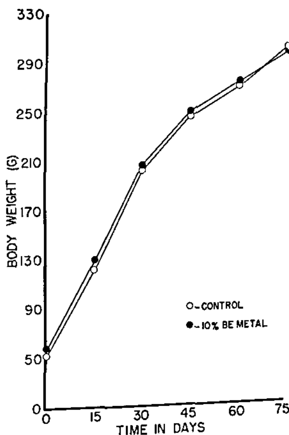


FIG 110 Growth curves of 2 male rats fed on a diet of which 10 per cent was beryllium metal.

2 3% Dietary Level

Effect on Growth Two male rats (130 gm initial weight, age 46 days) were fed a diet containing 2 3 per cent beryllium carbonate for a period of 102 days, at the end of which time these animals had average weight depressions of 53 gm when compared with the controls (fig. 108). At this dietary level the rickets-like condition did not develop (see fig 109).

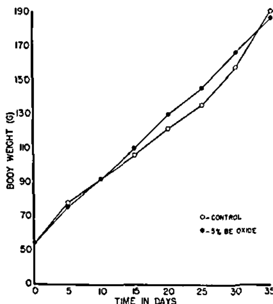


FIG 111 Growth curves of 2 weanling male rats fed for 33 days on a diet containing 5 per cent beryllium oxide

BERYLLIUM METAL

Two weanling male rats (age 27 days, average body weight 58 gm) were fed a diet containing 10 per cent beryllium metal for a period of seventy-five days Figure 110 shows that the experimental rats have grown equally as well as the controls.

Beryllium Oxide

Two weanling male rats (age 26 days, average body weight 54 gm) were fed a diet containing 5 per cent beryllium oxide for a period of 33 days Figure 111 shows that there was no effect on the growth of these rats when compared with the controls.

Summary

At a dietary level of 5 per cent, beryllium sulfate and beryllium carbonate completely inhibited growth of rats and caused some mortality. A rickets-like condition occurred in these rats. Food intake was reduced by about 50 per cent but this did not account for all growth inhibition as shown by a paired feeding experiment Return to stock diet after a prolonged period of ingestion of beryllium salt allowed rapid but not complete growth recovery. An early recovery from rickets occurred, followed by the appearance of a radiolucent area in the femur and tibia. Beryllium sulfate was more toxic to old rats than to weanlings, but with beryllium carbonate mature rats seemed to be more resistant than weanlings Beryllium carbonate at a level of 2 3 per cent of the diet caused some weight depression in rats Beryllium metal at a 10 per cent dietary level, and beryllium oxide at a 5 per cent dietary level did not affect the growth of rats.

Discussion

ARTHUR J VORWALD, M D.*

Mr. Maynard and his colleagues are to be congratulated on the exact manner in which they have conducted the experiments to determine the effect of beryllium ingested with the diet. I am glad to have their observations because the Saranac Laboratory has no controlled experiments concerning the feeding of beryllium However, our inhalation experiments have afforded some observations.

* Director, The Saranac Laboratory and The Trudeau Foundation, Saranac Lake, New York

We have noted a loss of weight in animals exposed to atmospheric suspensions of beryllium compounds sufficient to contaminate the food which the animals ate The loss was no more severe, however, than in animals subjected to other forms of dust. In other experiments, in which beryllium was injected intravenously or intraperitoneally, we have noted a decrease in weight during the active phase of the experiment. As soon as that phase was completed, when the animals were allowed to rest without repeated handling, they recovered

In many of our experiments we have noted sclerosis of the shaft of the long bones and some organization of the bone marrow Perhaps those changes were but a part of the picture of general hyperplasia of the lymphoid and hematopoietic tissues In this connection I should like to refer you to our experiments in which malignant tumors of bone have been produced following the intravenous injection of certain beryllium compounds including zinc beryllium manganese silicate, beryllium oxide, and beryllium phosphate

Further Discussion

DR. KLEMPERER The appearance of rickets in young animals fed on beryllium has at times been accredited to the fact that no phosphate can be absorbed I wonder whether you have data supporting this claim or denying it?

MR MAYNARD I realize that the literature has gone into that at some length, but I'm sorry we have no data on it

DR VORWALD Dr Klemperer, do you wish to comment on the influence of beryllium on phosphorus and calcium in the bones? Does beryllium replace phosphorus in the bones?

DR. KLEMPERER It all hinges on the question of solubility of beryllium phosphate As we understand it now, the formation of bone is probably due to the local liberation of inorganic phosphate No one has pertinent data on beryllium

CHAPTER 19

Certain Aspects of the Acute Toxicity of Beryllium Injected Intraperitoneally

HAROLD C HODGE, PH.D ,* WILLIAM L. DOWNS, AND ELLIOTT A. MAYNARD†

L.D $_{50}$ dose determinations based on 24-hour mortality were made for various beryllium compounds by intraperitoneal injections in rats and mice A few injections were also made in rabbits and guinea pigs. The results are given in the following tables

TABLE XXXII RATS (25 PER GROUP) INJECTED INTRAPERITONEALLY WITH VARIOUS BERYLLIUM COMPOUNDS

Compound	*Solution Saline (S) or Aqueous (A)*	*Sex*	*Age*	*L D 50 mg /kg.*
Be oxalate	(A)	♂	Mature	5
Be oxyfluoride	(A)	♀	Mature	13
Be oxyfluoride	(A)	♀	Weanling	42
Be sulfate-anhydrous	(A)	♂	Mature	50
Be perchlorate	(A)	♂	Mature	60
Be sulfate-hydrate	(A)	♂	Mature	110
Be sulfate-hydrate	(S)	♂	Mature	200
Be metal	(S)	♂	Mature	(no 24-hr effect from 500)
Be carbonate	(A)	♂	Mature	(no 24-hr effect from 500)
Be oxide	(A)	♂	Mature	(no 24-hr effect from 1000)

† Head, - ,
Project, University of Rochester

TABLE XXXIII MICE (50 PER GROUP) INJECTED INTRAPERITONEALLY WITH VARIOUS BERYLLIUM COMPOUNDS

Compound	Solution Saline (S) or Aqueous (A)	Sex	Age	LD₅₀ mg./kg.
Be oxyfluoride*	(A)	♀	Mature	33
Be sulfate-hydrate	(A)	♀	Mature	200
Be sulfate-hydrate	(S)	♀	Mature	300

* Injection of the LD 50 dose of 33 mg./kg. gave mortality of 57 per cent in mature mice and 22 per cent in weanling mice

TABLE XXXIV RABBITS INJECTED INTRAPERITONEALLY WITH VARIOUS BERYLLIUM COMPOUNDS

Compound	Solution	Dose (mg./kg.) and Effect
Be sulfate	(S)	2.6, no effect over prolonged period, 4.3 and 9.0, died 60 hr., 27, died 60 hr
Be sulfate	(A)	2.6, died 6 days, 4.3, died 5 days, 9.0 died 4 days
Be oxide	(A)	770, no effect over prolonged period
Be metal	(S)	1000, no effect over prolonged period
Be oxyfluoride	(A)	1, died 4 weeks, 3, died 6 days, 4, died 3 days

TABLE XXXV GUINEA PIGS INJECTED INTRAPERITONEALLY WITH VARIOUS BERYLLIUM COMPOUNDS

Compound	Solution	Dose (mg./kg.) and Effect
Be sulfate	(S)	5.1, 1.1, 22 days, 10.2, 1.6, 22 days, 20.4, 2.2, 4 days
Be oxide	(A)	1000, no effect over prolonged period
Be metal	(S)	1000, no effect over prolonged period

From the above data it may be seen that the soluble salts of beryllium are toxic to various degrees when injected intraperitoneally and that the insoluble salts are practically nontoxic when so administered. For some unexplained reason saline solutions were less toxic than aqueous solutions. Young (weanling) rats and mice were more resistant to the toxicity of beryllium compounds than were mature animals.

Discussion

MORRIS DWORSKI, M.P.H.*

In the Saranac Laboratory, the cellular response in the peritoneal cavity of the guinea pig has been employed routinely to determine the toxicity

* Bacteriologist, The Saranac Laboratory, Saranac Lake, New York

of industrial mineral dusts, utilizing the method described by Miller and Sayers.[420] The injected dust for the most part localizes in the anterior portion of the peritoneal wall and in the omentum There the progressive appearance of the gross lesion and the cellular reaction have been used as a basis for the classification of industrial dusts. This response falls



FIG 112 Intraperitoneal reaction of a guinea pig to 2 cc. of a 10 per cent suspension of "acid-treated dehydrated slag" 5 days after injection. The reaction consists of focal collection of polymorphonuclear leukocytes about a central area of necrosis

into three groups, absorption, inertness, or proliferation. The absorptive reaction manifested by calcite and gypsum, in which the dust disappears from the peritoneal cavity without the production of scar tissue, usually indicates a harmless dust, while a proliferative reaction, characteristic of various forms of quartz, is considered harmful. In the inert reaction, the dust is not absorbed, does not initiate cellular proliferation, or cause necrosis The nodule of dust becomes flattened in time, and the dust is carried over a large area of the peritoneum by phagocytes.

In the inert group one finds coal, silicates, silicon carbide, and aloxite. Gardner[219] reported that a few silicates, like true talc, black mica, and

some of the clay minerals have provoked chronic inflammation, but this reaction tends to retrogress after some months with no progression to a stage of true fibrosis Further, Dr. Gardner believed that the peritoneal tissue reaction to particulate dust may often be correlated with the results of inhalation experiments and with clinical observations



Fig 113 Intraperitoneal reaction of a guinea pig to 2 cc of a 2 per [illegible] hs after injec- [illegible] mononuclear

The technic is to inject a single 2 cc dose of a 10% suspension of particles, 1 to 3 microns in size, in 0 85% salt solution. The 1-3 micron fraction is obtained by sedimentation from ground material Animals are killed after one, four, eight, and twelve months. Occasionally an animal died soon after the injection, the time interval indicating the degree of acute toxicity However, in these instances, which occurred with several of the beryllium compounds, a sublethal dose must be injected in order to elicit a tissue reaction which may be interpreted according to the criteria of Miller and Sayers

A group of beryllium compounds have been tested in this laboratory

carbide were well tolerated and observed for periods up to one year. The cellular responses were comparable At four months beryllium oxide produced *an active* cellular proliferation which tended to be progressive about the dust mass (fig 114). It is a good example of the *monocytic type* of reaction Beryllium carbide at four months also demonstrated the

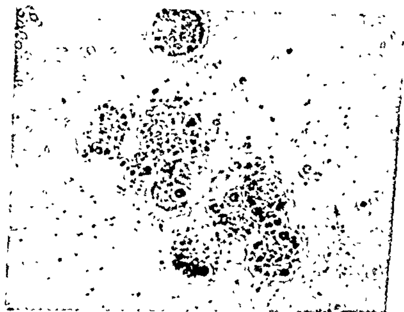


Fig 116 Supravital stained cells present in the intraperitoneal fluid

tral red and scattered fine dust particles Note the dust particles lying free in the fluid. × 1000

marked proliferation of active monocytes and giant cells, and a dense, fibrous capsule was present (fig 115) Here again one is inclined to suggest a possible similarity between the pulmonary granulomas following exposure to beryllium compounds and the persistent mass of proliferating monocytic cells present in the peritoneal tissues

It is difficult to use the Miller-Sayers classification to interpret the harmful pneumoconiotic potentialities of the beryllium compounds[429] These dusts incite a marked early inflammatory response followed by the stimulation of active monocytes, clasmatocytes, and foreign-body

giant cells, often with fibrous encapsulation of the dust mass. These compounds react differently than any inert dust so far observed. However, no true fibrosis or fibrotic nodules are produced and the character of the reaction is in no way comparable to the quartz response. Therefore, the reaction of these insoluble beryllium compounds may form the



FIG 117 Supravital stained cells present in the intraperitoneal fluid of a guinea pig from the same series represented by fig 116, but 10 days after injection The mononuclear phagocytes are now of the large macrophage type They exhibit globules of neutral red and masses of dust particles Note the absence of extracellular dust By this time practically all of the dust particles have been engulfed by mononuclear phagocytes

basis for an additional group in the interpretation of peritoneal tissue response

Present Experimental Work

Dr Vorwald has suggested that mention be made of an experiment now in progress to observe the cellular response in the peritoneal fluid following the injection of beryllium compounds The purpose of the experiment is (1) to note the distribution and type of free cells and to compare them with those fixed in the tissue, (2) to observe cell injury,

and (3) to measure the degree of phagocytosis Similar studies have been made with the tubercle bacillus and with quartz

Peritoneal taps are made at intervals and the cells are identified by

the procedure described

chnic the cells are kept

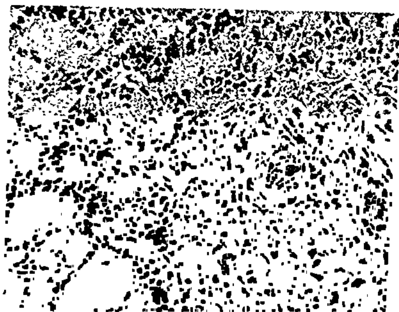


Fig 118 Omentum of a guinea pig 12 days after intraperitoneal injection of 50 mg of zinc beryllium silicate. The omental masses of particulate dust are surrounded by infiltrated mononuclear cells

alive. They are observed at 37° C in a warm box The nuclei do not stain A stained nucleus indicates either an injured or a dead cell. By the staining pattern of the cytoplasmic elements with neutral red, it is possible to identify with considerable certainty the monocyte, the clasmatocyte, the epithelial cell, and the various giant cells. The distribution of cells in a normal guinea pig's fluid is: polys 1 per cent, lymphocytes 20 per cent, monocytes 60 to 65 per cent, and the remainder eosinophils.

Following the injection of 50 mg. of $(Zn,Be)_2SiO_4$ suspended in 0.85% NaCl solution, there is an increase of the polys up to 50% for the first forty-eight hours The material consists of about 20 billion dust particles, 1 to 2 microns in size, and contains 2% BeO The poly- and the mono-

nuclear cells readily phagocytose the dust. Figure 116 shows monocytes with phagocytosed dust 24 hours after injection and free dust in the fluid. Beginning on the third day the active monocytes and clasmatocytes dominate the picture. The dust is readily and rapidly phagocytosed, as many as 40 to 50 particles being present in some cells. This compares to

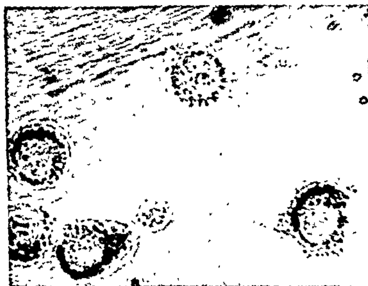


FIG. 119. Supravital stained cells present in the intraperitoneal fluid obtained from another guinea pig of the same series as in fig. 116, but 35 days after injection. The monocytes by this time appear normal and without stimulation as evidenced by the distribution of the supravital stained globules. The cells are now free of dust.

an average of 5 particles of quartz at this time. At ten days no free dust is seen in the fluid, though there are cells present with dust. There is no apparent injury to dust-laden cells. Figure 117 shows a supravital smear at 10 days, the clasmatocytic cell predominating, and fig. 118 is a fixed-tissue picture of masses of dust surrounded and infiltrated by monocytes and clasmatocytes in the omentum at twelve days.

At thirty-five days no epithelioid cells are seen, and the cellular distribution has returned to normal (fig. 119). In those animals injected with quartz, epithelioid cells appear at this time. From the observations at this time with $(Zn\,Be)_2SiO_4$ containing 27 BeO, it can be inferred

that the cells seen in the fluid are comparable to those found in the fixed tissue

It is interesting to speculate that the beryllium compound is sufficiently active to incite persistent proliferation of monocytic cells (granulomas), *but not potent* enough to convert the monocytic cell into an epithelioid cell, *as in tuberculosis, or to injure the monocyte so that it is replaced* by a hyaline nodule, as in silicosis

Further Discussion

MR DWORSKI Dr Hodge, how important are the acid radicals in the soluble beryllium compounds?

DR HODGE. The oxide was found to have a low toxicity in rats, with no deaths in twenty-four hours from 1000 mg. per kilogram of body weight. The fluoride is known to be toxic Less of the fluorides (13 to 42 mg per kilogram of body weight) was required to kill than of the sulfate (110 to 200 mg per kilogram of body weight)

Not being a cytologist, I am not competent to evaluate Mr. Dworski's *work, but it seems to be extremely valuable, it is a step in the right direc*tion I should like to compliment Mr. Dworski on this fine work.

MR DWORSKI I thank you, but credit for this work belongs to Dr. Gardner.

One more question, were the suspensions aqueous or saline, and how *much did you inject into an animal?*

DR. HODGE Are you inquiring about the concentration of the fluid, or the amount of fluid in the suspension? The concentrations were not the same for each compound. For the oxide, for example, a suspension of 50 mg *per cubic centimeter was employed*, whereas for the oxyfluoride the solution contained 10 mg. per cubic centimeter.

MR DWORSKI It is really the amount of fluid, rather than the concentration, that I am asking about

DR. HODGE. Our only rule is that in intraperitoneal injections we never give a rat more than about 8 cc in a single injection, or a mouse more than 1 cc.

CHAPTER 20

Preliminary Studies in the Toxicology of Beryllium: The Effect of Intratracheal Injection of Beryllium in Experimental Animals

CHARLES W LABELLE
AND
MARTHA REID CUCCI*

The experiments to be described in the following pages were intended to provide approximate answers to a number of general questions on the toxicology of beryllium, such as (1) the relative toxicity of certain industrially important compounds of beryllium, (2) the physiologic response of the animal body to beryllium, (3) the question of whether this response is an acute response to be studied in short-term experiments, or a chronic type of response requiring long-term studies, and (4) what physiologic variables reflecting this response can be measured in experimental animals The last question is especially important in a program of small animal research, since the literature relating to cases of suspected beryllium toxicity in human beings abounds with references to such clinical symptoms as pain, malaise, fatigue, respiratory sounds, and decreased vital capacity, all of which symptoms are difficult if not impossible to measure in experimental animals and which must be replaced by other tests more applicable to these conditions

The technic employed for most of these studies involved the introduction of solutions or suspensions of the materials to be studied into the lungs of white rats by injection into the lumen of the trachea This method has the advantage of localizing the material in the lung, which is the organ which most often serves as the portal of entry into the human body Another advantage is that the technic does not require the engi-

* From the Industrial Hygiene Section Division of Pharmacology, Atomic Energy Project, University of Rochester, Rochester, New York

[illegible] INJECTIONS OF BERYLLIUM METAL, BERYLLIUM COMPOUNDS, AND OTHER METALLIC COMPOUNDS

Dose† in mg./kg. body weight	Beryllium								Copper sulfate	Zinc sulfate	Mercuric chloride
	Metal	Oxide	Carbonate	Carbide	Fume	Fluoride	Oxyfluoride	Sulfate			
200	0/5	0/2			0/2						
175											
150	0/2										
125											
100	0/5	0/5	0/5	0/5							
75										2/2	1/1
50							2/2		2/2		
40								2/2			
30											
20									2/2	0/2	2/2
15						2/2	2/4	2/3			
10											
7.5						1/2				1/2	2/2
5.0							2/3		2/2		
4.0						0/2		0/2			
2.5						0/2			1/2	0/2	
2.0											0/2
1.50							2/4				
1.25								0/2			
1.00									0/2		
0.75						0/2					0/2
0.50							0/2	0/1	0/2		
0.25						0/2			0/2		
0.10							0/2	0/1			
0.075						0/2					
0.050											
0.025											
0.010											

Dose‡ in mg/kg body weight	Beryllium								Copper sulfate	Zinc sulfate	Mercuric chloride
	Metal	Oxide	Carbonate	Carbide	Fume	Fluoride	Oxyfluoride	Sulfate			
200	0/5				?						
175											
150	0/2										
125											
100	0/5										
75		0/2									1/1
50											
40		0/2									
30				0/5						2/2	
20									2/2		
15							2/2				2/2
10			0/5							0/2	
7.5						2/2			2/2		
5.0											2/2
4.0						1/2	2/4				
2.5								2/2		1/2	
2.0						0/2			2/2		
1.50											0/2
1.25						0/2	2/3				
1.00									1/2	0/2	
0.75								1/3			
0.50						0/2	2/4		0/2		0/2
0.25								0/2	0/2		
0.10						0/2	0/2		0/2		
0.075								0/2			
0.050						0/2	0/2				
0.025								0/1			
0.010						0/1		0/1			

* All values are expressed as number of animals dying per forty-eight hours

† Dose is expressed as mg material injected per kg body weight

‡ Dose is expressed as mg metallic component in material injected per kg body weight

neering studies prerequisite to the preparation of dusty atmospheres for inhalation studies. The method also permits the measurement of dosages with a precision impossible to attain in inhalation studies.

The Measurement of Minimal Lethal Dosage

When the action of a *foreign material on the living body is to be* studied, it is essential on the one hand to administer sufficient material to insure the production of a physiologic response, and equally essential on the other hand that the dosage be sufficiently small that the animal does not die before the response may be measured. It was, therefore, necessary to determine the approximate value of the minimal lethal dose for each compound studied The general procedure was as follows for soluble salts, a solution was prepared approximately isotonic with physiologic saline solution One and one-half cc. of this solution per kilogram of body weight was injected intratracheally into groups of 2 rats each. If either rat died, the solution was diluted 1.3 with physiologic saline and 1.5 cc per kilogram of the more dilute solution injected into 2 more rats This process was repeated using successive dilutions such as 1.3, 1 10, 1 30, 1 100, until a concentration was reached which killed neither animal within forty-eight hours For insoluble powders the material was suspended in saline at any convenient concentration and the suspensions diluted where necessary with physiologic saline. The number of animals dying within forty-eight hours is shown in table XXXVI. The effects of 3 other acidic salts are given for comparison The results may be summarized as in table XXXVII

The insoluble beryllium materials, beryllium metal, the oxide, carbonate, and carbide, thus exhibit a very low acute toxicity in the lung,

TABLE XXXVII APPROXIMATE MINIMAL LETHAL DOSE

	Mg salt/kg body weight	Mg metal/kg body weight
Metallic beryllium	over 200	over 200
Beryllium oxide	over 200	over 75
Beryllium carbonate	over 100	over 10
Beryllium carbide	over 100	over 30
Beryllium fluoride	15	8
Beryllium sulfate	10	1
Beryllium oxyfluoride*	2	0 7
Zinc sulfate	10	5
Copper sulfate	2	1
Mercuric chloride	1	0 7

* Assuming a formula of 2BeO 5BeF₂ and which closely approximated analytically determined values for Be

whereas the soluble beryllium salts, the fluoride, oxyfluoride, and the sulfate, have a toxicity comparable to that of the heavy metal salts. The deaths caused by the soluble beryllium salts appear to be the result of direct mechanical interference with normal lung function Therefore any

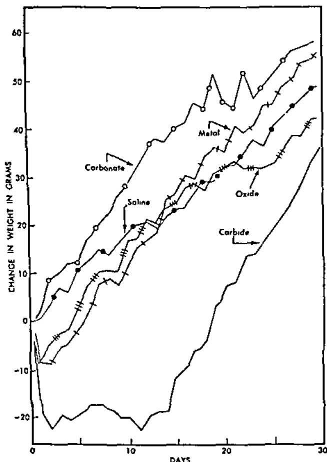


FIG 120 Change in weight of rats following intratracheal injection of insoluble beryllium materials

specific toxic effect of a particular beryllium compound would be obscured by such mechanical effects

Thirty Day Studies on Insoluble Compounds

Each of the insoluble beryllium materials was injected into groups of 5 rats at a level of 100 mg of the substance per kilogram body weight

neering studies prerequisite to the preparation of dusty atmospheres for inhalation studies The method also permits the measurement of dosages with a precision impossible to attain in inhalation studies.

The Measurement of Minimal Lethal Dosage

When the action of a foreign material on the living body is to be studied, it is essential on the one hand to administer sufficient material to insure the production of a physiologic response, and equally essential on the other hand that the dosage be sufficiently small that the animal does not die before the response may be measured. It was, therefore, necessary to determine the approximate value of the minimal lethal dose for each compound studied The general procedure was as follows· for soluble salts, a solution was prepared approximately isotonic with physiologic saline solution. One and one-half cc of this solution per kilogram of body weight was injected intratracheally into groups of 2 rats each If either rat died, the solution was diluted 1 3 with physiologic saline and 1.5 cc per kilogram of the more dilute solution injected into 2 more rats. This process was repeated using successive dilutions such as 1:3, 1:10, 1 30, 1 100, until a concentration was reached which killed neither animal within forty-eight hours For insoluble powders the material was suspended in saline at any convenient concentration and the suspensions diluted where necessary with physiologic saline The number of animals dying within forty-eight hours is shown in table XXXVI. The effects of 3 other acidic salts are given for comparison The results may be summarized as in table XXXVII

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TABLE XXXVII APPROXIMATE MINIMAL LETHAL DOSE

	Mg salt/kg body weight	Mg metal/kg body weight
Metallic beryllium	over 200	over 200
Beryllium oxide	over 200	over 75
Beryllium carbonate	over 100	over 10
Beryllium carbide	over 100	over 30
Beryllium fluoride	15	8
Beryllium sulfate	10	0 7
Beryllium oxyfluoride*	2	5
Zinc sulfate	10	1
Copper sulfate	2	0 7
Mercuric chloride	1	

* Assuming a formula of $2BeO \cdot 5BeF_2$ and which closely approximated analytically determined values for Be

whereas the soluble beryllium salts, the fluoride, oxyfluoride, and the sulfate, have a toxicity comparable to that of the heavy metal salts The deaths caused by the soluble beryllium salts appear to be the result of direct mechanical interference with normal lung function Therefore any

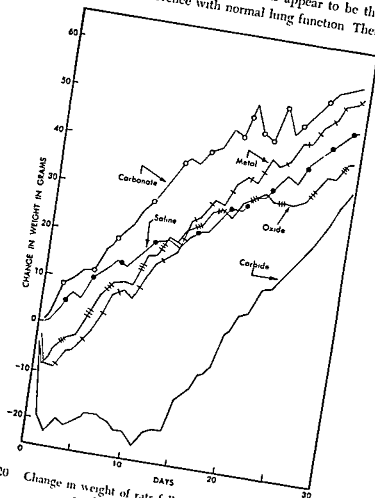


Fig 120 Change in weight of rats following intratracheal injection of insoluble beryllium materials

specific toxic effect of a particular beryllium compound would be obscured by such mechanical effects

Thirty Day Studies on Insoluble Compounds

Each of the insoluble beryllium materials was injected into groups of 5 rats at a level of 100 mg of the substance per kilogram body weight

Because an insoluble compound may require weeks or months before it is eliminated completely from the lungs, the animals were observed for thirty days. Weights were recorded daily, and white blood counts made at intervals of one or two days

The growth curves, each representing the mean values for a group of five animals, are shown in fig. 120 The only compound which showed

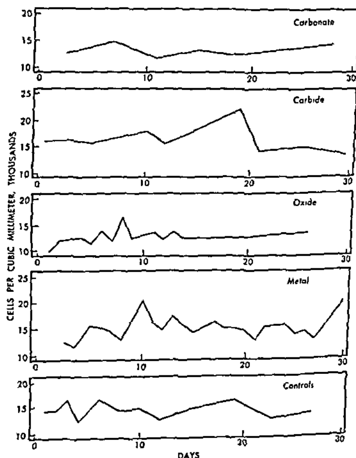


Fig 121 Count of white cells following intratracheal injection of insoluble beryllium materials

definite evidence of toxicity was beryllium carbide. Further examination of this compound showed that it decomposes slowly in water to yield acetylene, in a manner analogous to the decomposition of calcium car-

bide.* The odor of acetylene could be detected readily in the exhalations of the rats injected with beryllium carbide, and it is probable that the response visible in the growth curve is related more directly to this reaction than to any more specific property of beryllium per se

The curves of the white blood counts for these same groups are shown in fig 121. The animals treated with beryllium carbide showed some evidence of abnormality, the mean leukocyte count rising at one point to 22,000 cells per cubic millimeter Somewhat curiously, this peak occurs at a *time when the weight curve would indicate that the animals had* returned to a normal growth rate No explanation is offered for this fact

In addition, the animals injected with metal powder show unusually high leukocyte counts, peaks occurring at ten days and at thirty days Re-examination of the data and several repetitions of the experiment revealed that the peaks were produced because one or two animals attained extremely high values, raising the mean for the group significantly In a group of 20 animals being studied daily, 2 reached maxima of 39,000 and 47,000 cells, respectively, at five days, a third reached 34,000 at ten days, while 7 others, followed daily for forty days, never exceeded 21,000 cells per cubic millimeter Growth curves were equally inconsistent, 1 animal increased in weight by only 10 gm in 200 days, whereas 10 others increased 70 gm in 30 days In spite of these inconsistencies, the fact remained that at least some animals showed incontrovertible evidence of toxic damage

Long-Term Toxicity Studies on Beryllium Metal

In view of the suggestive findings in the short-term studies described above, a number of animals were injected with 100 mg of beryllium metal each per kilogram of body weight and studied for periods in some instances nearly as long as a year

During this time the hematologic program was expanded considerably, and a large number of blood counts was tabulated For purposes of orientation, a statistical analysis of a portion of these data is presented in table XXXVIII A total of 261 counts were recorded for animals which had received beryllium or its compounds, and 132 counts for animals which had not received beryllium The treated group contained animals

* Small amounts of beryllium carbide kept in water in a closed test tube for two or three days release sufficient acetylene to produce a flame when ignited. The odor of acetylene is pronounced

TABLE XXXVIII MEANS AND STANDARD DEVIATIONS OF HEMATOLOGIC VARIABLES IN A GROUP OF CONTROL AND BERYLLIUM-INJECTED RATS

Variable	*Group*	*No of determinations*	*Mean*	*Average deviation from mean*	*Fiducial limits (1%)*	
No of W B C	Control	132	13 2	4 26	25 98	0 42
	Treated	261	13 9	4 49	27 37	0 43
% polymorphonuclears	Control	132	28	8 5	53 3	2 5
	Treated	261	37	13 1	76 3	0
% eosinophils	Control	132	3	2 5	10 5	0
	Treated	261	4	3.7	15 1	0
% lymphocytes	Control	132	69	8 7	95 1	42 9
	Treated	261	59	12 8	97 4	20 6
No of polymorphonuclears	Control	132	3 8	1 76	9 08	0
	Treated	261	5 3	3 17	14 81	0
No of eosinophils	Control	132	0 35	0 332	1 346	0
	Treated	261	0.51	0 513	2 049	0
No of lymphocytes	Control	132	9 1	3.14	18 52	0
	Treated	261	8 1	2 69	16 17	0 03

that were, in addition, subjected to a variety of physiologic stresses such as infections, exercise, and exposure to heat and cold. The control group received the same secondary treatment but no beryllium Thus the groups were practically identical with respect to all conditions except beryllium

TABLE XXXIX HEMATOLOGIC CHANGES IN RELATION TO OTHER SIGNS OF TOXIC DAMAGE IN ANIMALS INTRATRACHEALLY INJECTED WITH BERYLLIUM

Group	*No of Determinations*	*No of WBC*	*% Polymorphonuclears*	*% Eosinophils*	*% Lymphocytes*	*No. of Polymorphonuclears*	*No. of Eosinophils*	*No. of Lymphocytes*
Controls	132	13 2	28	3	69	3 8	0 35	9 1
All rats exposed to beryllium	261	13 9	37	4	59	5 3	0 51	8 1
Exposed rats during periods of normal growth	65	12 20	29 4	2 8	63 2	3 61	0 33	8 30
Exposed rats during periods of weight loss	23	14.98	49 2	0 52	50 2	7.17	0 10	7 55
Exposed rats during final week before death	20	15 89	48 8	0 70	50 1	7 47	0 14	8 36

exposure, and any differences in the findings may be ascribed to this exposure Although the deviations were high, the means for the two groups were nearly identical with the exception of the values for relative and absolute polymorphonuclear cells, which were shifted by one standard deviation.

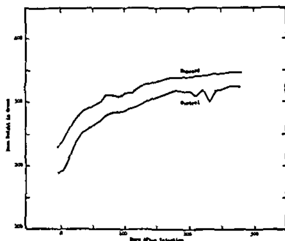


FIG 122 Curves showing growth of rats after injection of 100 mg of metallic beryllium per kilogram of body weight

In table XXXIX the data is shown broken down into subgroups Here the shift in the polymorphonuclear count is very striking particularly in those animals which were losing weight or dying From these data it may be assumed that exposure to beryllium is associated with a rise in the polymorphonuclears of the blood The fact that this rise may or may not be sufficiently great to affect the total white cell count undoubtedly explains some of the inconsistencies observed in the white cell counts described in the preceding section

Figures 122 and 123 show the growth and mortality curves for a period of 250 days for a series of 12 beryllium-injected rats and 10 control animals injected intratracheally with saline solution Growth appears to be essentially normal, at least for the first 200 days, the fluctuations in the last 50 days are the unavoidable effect of the loss of animals from a small residual group The mortality curve indicates that 75 per cent of the exposed group died, compared with none of the control group Since

these rats were less than a year old at the end of the period described, and since normal mortality from "old age" is from 9 to 12 per cent at one year for rats in our colony, this high mortality rate cannot be ascribed to "old age." Several other series which have been similarly treated with beryllium, but for shorter time intervals, are confirming the earlier portions of this mortality curve.

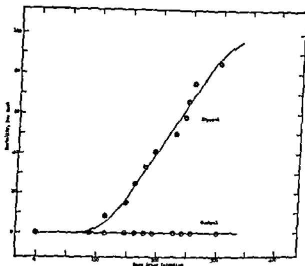


FIG 123 Mortality in rats after injection of 100 mg of metallic beryllium per kilogram of body weight.

A limited amount of pathologic data is available for these animals up to about 100 days.* When injected into the lungs of rats, beryllium metal induces an inflammatory reaction sufficiently severe to lead to necrosis of tissue The metal is gradually removed from the lung parenchyma and appears largely in the peribronchial lymphatics, some reaching the tracheobronchial lymph nodes (where its presence has been confirmed spectroscopically) No permanent scarring, fibrosis, or granulomatous lesions in the lung have been produced up to 100 days, and no changes in other organs of the body were demonstrable The ultimate fate of the injected metal is still uncertain from the autopsy material so far available.

The deaths occurring in this series of animals appeared to follow a

* For this we are indebted to Dr James K Scott of the Pathology Section of the Atomic Energy Project at the University of Rochester.

reasonably consistent pattern. The terminal weights of some of the dying animals are shown in fig 124 where the individual animal weights are plotted for the 30 days preceding death It will be seen that although the group as a whole increased in weight (fig 122), the individual animals lost weight consistently for the month preceding death The

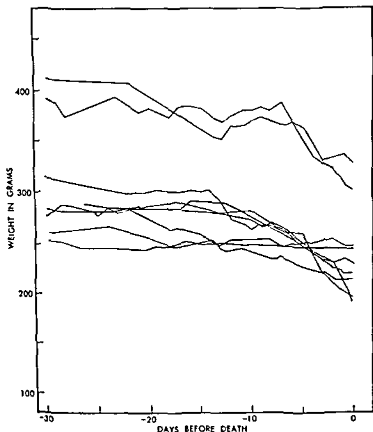


FIG 124 Weight changes in rats of figs 122 and 123 for the month preceding death

relative and absolute polymorphonuclear counts for the same period are shown in fig 125 The black circles for the exposed animals represent counts made at the times indicated, and the light circles represent control counts made on approximately the same calendar dates. Whereas the separation between exposed and control animals was not without some

overlapping, the tendency toward high polymorphonuclear counts in these animals was well marked.

Concurrently with these changes, the animals tended to develop dyspnea, severe râles, and increased irritability. One deviation from normal behavior was hyperexcitability during handling. The most con-

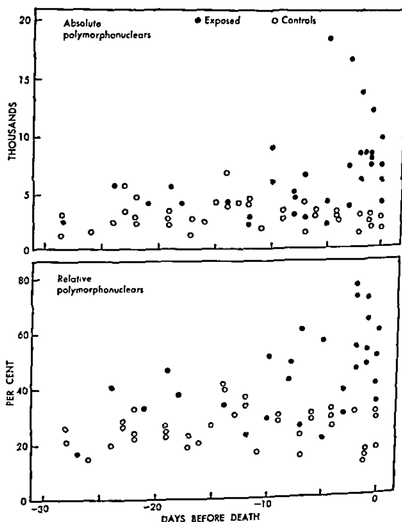


Fig 125 Relative and absolute polymorphonuclear counts of rats of figs 122 and 123 for the month preceding death

sistent gross postmortem finding was severe lung damage involving various combinations and degrees of edema, hemorrhage, consolidation, and ulceration

The Effect of Secondary Factors on Beryllium Toxicity

Because the time intervals involved in the preceding study represent so large a fraction of a rat's total life span, a series of short-term experiments have been carried out to determine whether a combination of beryllium exposure with other common debilitating agents might cause a more rapid development of the damage described above Among the secondary agencies studied were enforced activity, daily exposure to high temperatures (110° to 120° F.), daily exposure to low temperatures (20° to 40° F), infection with various pathogens such as salmonella, pneumococcus, and pertussis, exposure to uranium dusts, exposure to hydrogen fluoride vapors, repetitive exposure to beryllium in an attempt to produce anaphylaxis, and the use of oils rather than saline solution as a carrier for the metal powder Only a half-dozen deaths resulted from the entire study, comprising nearly 150 animals, and so far in no case was unequivocal evidence obtained which would indicate a specific relationship of any magnitude between any of these agencies and the toxic effects of beryllium itself

Conclusions

Soluble beryllium salts, when introduced into the lungs of rats, exhibit lethal properties comparable to those of the heavy metals such as copper, zinc, and mercury Insoluble beryllium compounds are much less toxic when so introduced Metallic beryllium and possibly other beryllium compounds as well produce a more chronic type of lung damage of an apparently nonspecific type which eventually leads to the death of the animal The lung damage is apparently not identical with the human types of damage No method has been found by which this chronic process may be appreciably hastened

Summary

Beryllium and certain of its industrially important compounds have been administered to rats by the intratracheal route as an experimental introduction to the field of inhalation toxicity of beryllium dusts The tracheal route permits known amounts of toxic materials to be introduced directly into the lungs of animals and allows a more rapid appraisal of pulmonary toxicity than is possible by the more cumbersome inhalation studies

In the absence of information on the nature of beryllium poisoning in animals via the lung, the tracheal studies were designed to supply infor-

mation on: (1) the relative toxicities (M.L.D.) of insoluble beryllium dust suspensions and certain soluble beryllium compounds, (2) the type of physiologic response, whether acute or chronic, (3) the variables which might offer a means of appraising beryllium toxicity.

The forty-eight-hour M.L.D for beryllium metal dust and the insoluble beryllium compounds (the oxide, the carbonate, and the carbide) were all greater than 100 mg. of material per kg of body weight; that of the soluble compounds (beryllium fluoride, sulfate, and oxyfluoride) was 15, 10, and 2 mg of salt per kg of body weight, respectively. These values were comparable to the M.L.D. by the tracheal route of such acidic salts of heavy metals as copper and zinc sulfate, and mercuric chloride. It has been concluded accordingly, because of the similarity in response, that the deaths from soluble compounds were caused by direct mechanical interference with normal lung function rather than by any specific toxic effect of beryllium per se.

The type of response was distinct for the soluble and insoluble beryllium materials The soluble beryllium compounds produced acute toxic death On the other hand, the insoluble beryllium materials produced effects of a chronic nature Deaths from the latter group of materials did not occur before the one hundredth day following exposure and became most prominent between this period and the three hundredth day

In addition to decreased growth response, hematologic changes gave the greatest promise of indicating current injury from beryllium Changes in the blood picture were confined chiefly to increase in the polymorphonuclear leukocytes. These findings were by no means uniform as was characteristic of beryllium poisoning in general in animals. At death, pathologic changes in the lungs of rats given beryllium metal dust consisted of an inflammatory reaction and in some instances necrosis.

At present, no animal host or method of producing the pulmonary type of injury in animals identical with that of men has been found, despite the fact that several animal species have been investigated and numerous methods of modifying the pulmonary exposure have been tried.

Discussion

ANTHONY B DELAHANT*

This presentation by Mr LaBelle is of considerable interest to me because it parallels to some degree the work in the Saranac Laboratory, particularly in regard to what we have done with the introduction of dust suspensions or solutions of beryllium by this injection route The guinea pig rather than the rat has been our species of choice, chiefly because of our wider experience with this animal in investigations with other minerals

Our dosage has varied to some degree, ranging from 50 mg to 150 mg per animal. The weight of animal was approximately 600 gm. The injections were administered, in most instances, in equally divided doses at weekly intervals for three weeks The toxic reaction that was manifest between injection periods usually gave indication as to the size of dose that should be used

Many of the agents used had their sources in the various phases of the beryllium industry and included beryllium oxide, beryllium hydroxide, beryllium stearate, beryllium nitrate, zinc beryllium silicate, beryllium salvage tube powder, dross, frit, and the acid-treated slag

As the tissue response in these animals is discussed in detail by Dr Vorwald,† suffice it to say here that although no attempt was made to establish the amount of the minimal lethal dose, it was generally felt that the soluble beryllium compounds produced more acute reactions, while those of the insoluble materials tended more towards chronicity In this we concur with Mr LaBelle's findings

I believe some comment should be made here as to the disadvantages as well as the advantages of this method It is agreed that dosage may be controlled to some degree, doubtless with far greater precision than is attainable with inhalation technics Our animals however, are injected without anesthesia, and although we use a special 6-inch, 20-gauge needle inserted to the bifurcation of the trachea it is felt there is some loss of material through subsequent cough And again since there is a tendency to produce massive accumulation of dust in localized areas, dispersion of the material is not accomplished as in inhalation

* Research Associate, The Saranac Laboratory Saranac Lake, New York

† See Chapter 25 (Ed)

Further Discussion

DR. RICHARDSON. This point may be taken up later on, but I would like to bring it up now for the reason that one case of delayed pneumonitis, though consuming an adequate diet, developed marked scurvy, and had bleeding and swollen gums, and purpuric spots. We put him on 150 mg. of ascorbic acid a day, which brought about clearing in a few days, and the platelet count was normal.

I had hoped that, when the question of vitamins was brought up this morning, someone might mention the other vitamins in relation to some of these animals that were used for experimental purposes, and I would like to know if any of these animals could react as a human. I have also observed that there was a marked deficiency in B-complex and also in vitamin A in the delayed type of pneumonitis and that they require a large amount in spite of adequate diet I just bring that up as a suggestion.

DR. HOWLAND. Thank you very much It is also in parallel with a comment made to me: that all liver function tests, by and large, depend upon the state of nutrition of the individual at that time. If we carry out a great number of rather uncontrolled liver function tests, we are going to have a state of chaos, where there is now only a state of confusion. I think that is really pertinent.

There is comment which I think Mr. LaBelle neglected to make As a part of his work he made a tentative study of the various factors or agents which might contribute toward the development of beryllium toxicity in animals.

MR. LABELLE When we started to investigate this long term damage, it was a nuisance to wait 300 days for an answer, so we started to try all sorts and kinds of agents. Among them were exposure to heat, exposure to cold, malnutrition, enforced exercise, various and sundry types of infection—pertussis, pneumococcus, and three or four others, including other materials that we happen to know a little about, like the uranium compounds. Generally speaking, we got absolutely nowhere. No experiment showed clear-cut evidence that we had speeded up the beryllium process one bit

DR HOWLAND: I think that is extremely important evidence.

DR SHELESNYAK: I just want to know if, in the series of extra factors, exposure to X-rays was used as a possible accelerating agent.

MR LABELLE Not as a direct experiment, but we did have animals of which we took X-ray pictures, in some cases every two or three days, over a protracted period. We are watching them and checking to see whether the X-ray made a difference in the results, it didn't seem to We didn't go into it any farther than that

Initial Studies of the Toxicity of Inhaled Beryllium Sulfate Dust and Beryllium Metal Fume

GEORGE F. SPRAGUE, CHARLES W. LABELLE, ALTON G. PETTENGILL, AND HERBERT E. STOKINGER, PH.D.*

Beryllium Sulfate Study

An inhalation study of the toxic effects of a soluble beryllium salt, the sulfate tetrahydrate, has been performed on 56 animals representing six species Following a conditioning period of two weeks, the animals were exposed six hours daily in a dust inhalation chamber for a period of two weeks, a total of sixty-six exposure hours. The concentration of dust approximated 90 mg. of hydrated beryllium sulfate per cubic meter of air, expressed as the cation, 4 5 mg Be/m.^{3} or 0 5 millimol Be/m^3

For reasons of chamber space limitations, not all the animals could be exposed concurrently Three individual exposures were made under similar conditions of time and dust concentration Mortality, weight response, and histologic changes were used as measures of toxicity in one study, differential blood counts and biochemical findings in addition were employed in another study In the third study, in which 2 dogs only were used, several biochemical tests for possible beryllium injury were employed as well as thorough hematologic studies, in an effort to establish critical diagnostic aids for beryllium poisoning as well as the route and site of beryllium damage

Materials and Methods

The chamber (fig 126) in which the animals were exposed was a 31-inch transite-lined cube with a capacity of 17.8 cu. ft. (505 liters). The animals shown in the chamber in fig. 126 occupied a volume of approxi-

* Head, Industrial Hygiene Section, Division of Pharmacology, Atomic Energy Project, University of Rochester, Rochester, New York

mately 19.7 liters or 3.9 per cent of the chamber space. Also visible is the type of cage employed for exposure of the animals. Whenever practicable, partitioned cages were used to insure individual exposure of the animals. The photograph, at the end of a day's operation, shows a considerable

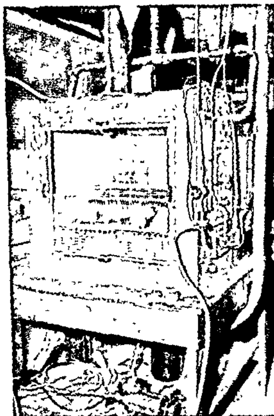


Fig. 126. Chamber in which animals were exposed to beryllium sulfate dust.

deposit of the sulfate on the cages, around the opening of the doorway (the door has been removed) and on the rear observation window.

Figure 126 also shows most of the valves and manometers used to control the dust concentration in the chamber. The valve shown at the right center of the open doorway is used to adjust the air velocity during sampling of the dusty atmosphere. The manometer to the right of the

valve indicates the hydrostatic pressure of the sampling line At the middle right of the unit is one of the ports where the sampling line may be inserted Below the sampling port is an inclined manometer to indicate the rate of air flowing through the chamber at any given time. The vertical manometer at the extreme right of the chamber is used to indicate the rate of nitrogen flow through the dust feed Air from the centrally located filtering and refrigeration unit is introduced into the chamber at the base of the unit at the rate of 18 cu. ft. per minute, thus permitting one air change per minute. A fan, to aid in the even distribution of the air and dust in the atmosphere, is located in the ceiling of the unit. The air-evacuation flues are located on the side walls near the ceiling. Before being drawn into the central rotoclone, the exhausted air is drawn through a scrubber (the cone-shaped portion of which is visible above the unit) using water as the scrubbing medium Scrubbing traps the beryllium sulfate and prevents its liberation into the air in or around the building.

The type of *dust feed* found most satisfactory in producing the desired concentration was the rotating barrel feed of 3-inch diameter (shown below the unit in fig 126) A 1/20 horsepower motor rotated the barrel on its horizontal axis so that the dust came to the apex of the conical cylinder. Here it was forced into the feed line by a stream of dry nitrogen and carried up into the chamber At the base of the chamber the air intake line and feed line converged, thus blowing the finely divided dust into the chamber A constant check of the concentration was maintained by taking frequent samples (from 9 to 15 per day) of the chamber atmosphere The concentration in terms of milligrams of $BeSO_4 \cdot 4H_2O$ per cubic meter of air was determined gravimetrically.

Because of the somewhat hygroscopic nature of this beryllium compound, considerable difficulty was encountered in preparing a dust whose median particle size was no greater than 2 microns. The technic developed involved drying the beryllium salt for at least twenty-four hours in a vacuum desiccator, before passing it twice through a micropulverizer. Only the dust that passed a 230-mesh sieve was ultimately used in the feed, which was filled twice daily with vacuum-dried dust. Between each step of the dust preparation, the material was kept in evacuated desiccators Beryllium sulfate tetrahydrate, left exposed to the air, completely dissolves in the absorbed water, yielding a saturated solution of approximately pH 1 0

It was impossible to maintain at all times the desired concentration of 90 mg of the salt per cubic meter of air in the inhalation chamber. A weighted mean concentration determined gravimetrically from 137 samples was 84.3 mg/m.³ with a standard deviation of 36.6 The extreme values were 13.2 and 267.0 mg/m³. Ninety-four of the concentration values were between 50 and 135 mg/m.³.

Toxicity Criteria

The types of data collected and analyzed included mortality, weight response, micropathologic and hematologic findings, and biochemical changes The blood determinations included nonprotein nitrogen, urea nitrogen, amino acid nitrogen, serum protein, sugar, albumin-globulin ratio, bromsulfalein and fibrinogen levels. The urinary studies included sugar, protein, and amino acid nitrogen/creatinine ratio Table XL lists the number of animals of each species used in each of the toxicologic observations Obviously, the animals of the various groups, particularly the dogs, were used for more than one test

TABLE XL NUMBER OF ANIMALS USED IN TESTS FOR TOXICITY CRITERIA

Criteria Studied	*Dog*	*Rabbit*	*Guinea Pig*	*Mouse*	*Hamster*	*Rat*
Mortality	2	3	14	20	7	10
Weight response	2	3	14		7	10
Biochemistry						
Blood						
NPN	2	3				
Urea nitrogen	2					
Amino acid nitrogen	2					
Sugar	2					
Serum protein	2					
Albumin globulin ratio	2					
Urine						
Sugar	2					
Protein	2	3				
Amino acid nitrogen Creatinine ratio	2					
Hematology	2	3				10
Pathology						
Terminal	2	3	14		5	8
Dying animals				20	1	2
Liver Function Tests						
Fibrinogen levels	2					
Bromsulfalein retention	2					

Results

Mortality. Figure 127 is a graphic representation of the mortality rate for the three species in which deaths occurred. It shows that all of the 20 mice exposed in the chamber died before the termination of the experiment, an LD_{50} occurring on the seventh calendar day. Because

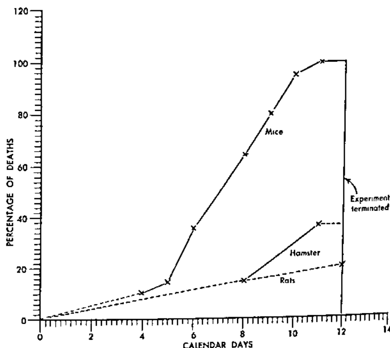


FIG 127 Mortality curves of mice, hamsters, and rats exposed to 90 mg/m³ of beryllium sulfate

of the high mortality rate observed in this species, 10 additional mice were exposed for two days before the termination of the study. Two of these 10 mice died following the second day of exposure. Two of 10 rats died and 2 of 7 hamsters died as a result of the exposure The broken lines on the graph indicate the time from the start of exposure until the first death occurred, the broken line indicating the uncertainty in the length of time of exposure required to cause the first death There were no deaths among the dogs, rabbits, or guinea pigs

Symptoms The outward symptoms and reactions to the beryllium dust differed markedly for each of the species At the conclusion of the first six-hour day of exposure, the eyes of the mice were irritated, but were

improved by morning While undergoing treatment the mice were hyperirritable and more active than normal, and before death usually went into convulsive spasms. The eyes of 6 of the 14 exposed guinea pigs showed definite signs of cataract formation The ocular opacity of these animals developed after two days or twelve hours of exposure. A few rats' eyes appeared hemorrhagic and the breathing of some indicated râles.

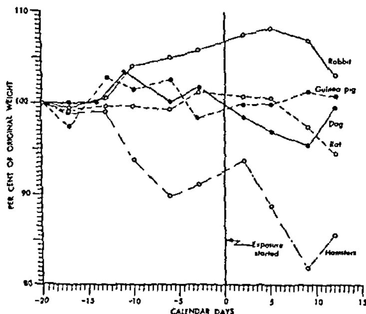


FIG. 128 Per cent weight change of animals exposed to 90 mg m³ of beryllium sulfate

It was originally planned to expose the 2 dogs for two weeks and then hold the animals for a year in order to follow the effects of the beryllium exposure, however, such serious ocular injury and periorbital lesions occurred (Plate IV, A) that it appeared probable that at least one of the dogs would die from subsequent infection These lesions were aggravated by the animal scratching its eyes with its paws and also by rubbing its head and eyes against the metallic mesh of the cages. This action caused the left eye to protrude half an inch, while the ulcer about the right eye, at autopsy, burst upon the application of slight pressure Other less extensive but well-defined ulcerative lesions (Plate IV, B) developed

on the legs and body of the *second dog*. A small cataract was noted on the left eye of this animal. The highly acidic character of this beryllium compound, no doubt, was responsible for the start of ulcerative lesions observed in these exposed animals.

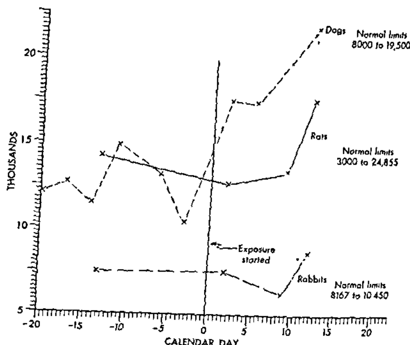


FIG 129. Count of white blood cells of dogs, rabbits, and rats exposed to 90 mg./m³ of beryllium sulfate.

The beryllium sulfate caused fewer discernible external symptoms in the rabbit and hamster than in the other species. A hypersensitivity and nervousness were noted in the hamster, but no outward changes were observed in any of the three rabbits.

Weight Response. The weight response data showed that all of the animals, with the exception of the guinea pigs (fig 128), were adversely affected. There was less fluctuation in the weight of the guinea pigs during the exposure period than during the two-week conditioning interval. The rabbits lost 5 per cent in weight, while the hamster and the rat lost

PLATE IV

A Dog suffering from severe periorbital lesions following exposure to beryllium sulfate dust *B*. Dog which developed ulcerative lesions over the legs and body following exposure to beryllium sulfate dust

A

B

Caption on facing page

11 per cent of their weight during the period of exposure. The dogs, as shown in fig. 128, were 5 per cent below their original weight but regained this by the time the exposure terminated. Since no mice survived, complete weight data are not available, but it was noted that the mean weight declined for the mice surviving until the ninth calendar day.

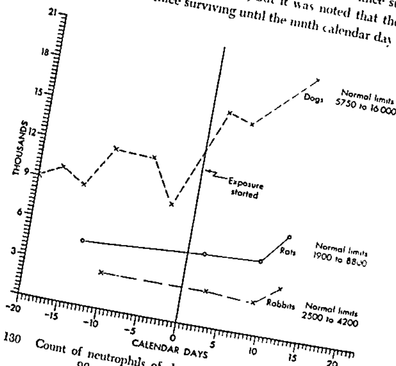


FIG. 130. Count of neutrophils of dogs, rats, and rabbits exposed to 90 mg./m³ of beryllium sulfate.

Hematologic Response. Of 9 hematologic blood variables studied in the dog, rabbit, and rat, (figs. 129, 130) only the leukocyte and the absolute neutrophils* showed any significant change. This constituent showed a marked rise for the three species between the ninth and twelfth day of the experiment, however, values from normal animals have occasionally been recorded that were higher than any noted in this study. The red blood count showed little change.

Clinical Chemical Response. The clinical chemical values indicated that renal damage occurred in the rabbits during the second week of the

* Obtained by multiplying the percentage of neutrophils by the number of white blood cells.

experiment (fig. 131). During the two-week conditioning period and the first week of dust exposure, the mean N.P.N. values were unusually constant for rabbits, but in the second week the values rose to 78 mg. per 100 cc of blood and were more than 70 mg. per 100 cc. at the termination The rabbit urinary protein values showed much the same trend, with the

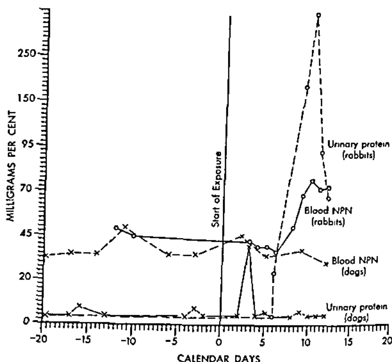


FIG. 131 Analysis of blood and urine of rabbits and dogs exposed to 90 mg./m³ of beryllium sulfate

first positive value being recorded on the sixth day and a high mean of 350 mg per 100 cc of urine on the tenth day. The final protein value was 80 mg. per 100 cc. This decreased proteinuria may be an indication of regeneration of the renal cortical tubules

The biochemical findings in the dog failed to reveal any indication of renal or hepatic injury during the course of exposure As seen in fig. 131, a higher N.P N value was obtained for the dogs during the conditioning exposure than was found at any time after the dust was introduced into the chamber. The high urinary protein value found on the second day of exposure was probably caused by contamination of the specimen. The

other urinary constituents failed to show any results that were indicative of kidney impairment. All of the amino acid nitrogen/creatinine ratios and urinary sugar values were definitely normal.

Biochemical evidence of a negative nature was obtained from all of the analyses of the blood of the dogs for sugar, urea nitrogen, amino acid nitrogen, bromsulfalein, and serum protein, as all of these values were within normal limits and showed no trends from a time study viewpoint. The albumin/globulin ratio results showed an upward trend toward the end of the experiment. The rise was caused by a decrease in the globulin fraction of one of the dogs with a corresponding decrease being noted in the fibrinogen level, which is a globulin protein, of the blood.

Micropathology. The micropathologic results,* like the data obtained by means of the other toxicologic criteria, showed a marked species differentiation yet reasonable similarity within each of the species. Seventeen of the 20 dying mice were autopsied and microscopic sections of the organs were made. Because considerable autolysis had occurred between the time the animal died and the time when sections could be taken, the lung and kidney sections, two organs of importance in beryllium sulfate poisoning, were of little value so far as this species was concerned. The liver of the mouse showed definite lesions that were comparable to those seen when lethal doses of beryllium sulfate were administered intravenously or intraperitoneally. The lesion was a central or midzonal necrosis of liver cells, with the amount of cellular necrosis varying with the time of death of the animal. The last 4 mice to die had no lesions of this type indicating complete regeneration of the liver had occurred by the ninth calendar day.

The rabbits showed the most severe and widespread pulmonary lesions of the species used in this experiment. These lesions consisted of a fairly widespread edema, some foci of atelectasis, and some inflammatory exudate in the lumina of the terminal bronchi. The kidneys of the rabbits showed considerable necrosis of the tubular epithelium particularly in the distal portion of the proximal convoluted tubule and in the descending loop of Henle. Regeneration and necrosis can be seen occurring in the same kidney. No lesions were found in the glomeruli. The other organs of

* For this information we are indebted to Dr. James K. Scott of the Pathology Section of the Atomic Energy Project at the University of Rochester.

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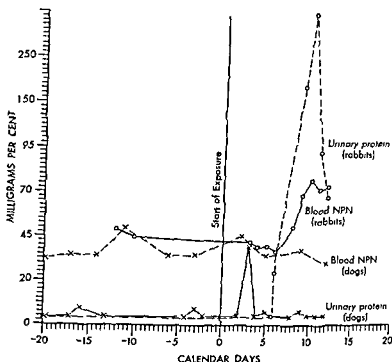


FIG 131. *Analysis of blood and urine of rabbits and dogs exposed to 90 mg /m³ of beryllium sulfate.*

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the rabbit, including the eye and liver, failed to show any remarkable changes.

The guinea pigs showed the fewest histologic changes of any of the species, the lesions being limited to the lung and the eye. The lung lesions were similar to those noted in the rabbit but were much less extensive and less severe The eyes of most of the guinea pigs showed changes consisting of conjunctivitis and keratitis. All of these animals showed an inflammatory reaction at the limbus.

The injury to the hamster was almost entirely limited to the lung, consisting chiefly of edema accompanied by varying amounts of hemorrhage of the alveolar sacs None of the other organs of the hamster had any changes that could be attributed to beryllium poisoning.

Two rats died on the final day of the experiment. Whereas the liver sections showed no necrosis, the cells lining the kidney tubules showed numerous lesions. The most extensive changes found in the sacrificed animals occurred in the lungs and kidneys The pulmonary change most prominently seen was a rather marked edema which was accompanied by a moderate infiltration of neutrophils and monocytes. The kidney damage seen in the rat was much like that noted in the rabbit. There was no liver damage in this species.

TABLE XLI THE EFFECTS OF $BeSO_4 \cdot 4H_2O$ ON THE TISSUES OF EXPOSED ANIMALS

	Mouse	*Rabbit*	*Guinea pig*	*Hamster*	*Rat*
Lung	?	4+	1+	2+	3+
Liver	4+	0	0	0	0
Kidney	?	4+	0	0	4+
Eye	0	0	4+	0	0

Table XLI summarizes the histologic findings in the various species. In this table the higher numbers represent the greater amount of tissue damage It is evident that the guinea pig and hamster seem to be the most resistant species and the rabbit and mouse the most sensitive. No explanation is offered for the lack of finding of hepatic injury in species other than the mouse although hepatic injury was observed in mice that died early in the exposure.

The histologic findings for the 2 dogs are not yet available, however.

the gross pathologic examination failed to show any marked damage by the $BeSO_4 \cdot 4H_2O$

Summary

Data have been collected and evaluated on 2 dogs, 10 rats, 3 rabbits, 14 guinea pigs, 20 mice, and 7 hamsters exposed to a high concentration of $BeSO_4 \cdot 4H_2O$.

The most striking feature of the study was the marked species difference with respect to most of the toxicologic criteria employed Thus, all of the 20 mice died before the termination of the experiment, the histologic findings showed marked pulmonary damage in all of the species, hepatic damage in the mice, ocular lesions in the guinea pig and dog, renal necrosis in the rabbit and rat The micropathologic findings confirmed the biochemical observation that renal impairment had occurred in the rabbit, however, the clinical chemical observations failed to reveal any significant indication of renal or hepatic injury in the dog.

The only consistent result observed in all species was the marked rise of the leukocyte and absolute neutrophil count in the dog, rabbit, and rat The erythrocyte count for the three species was most constant throughout the period of exposure

The highly acidic nature of the beryllium sulfate tetrahydrate was the primary cause of the ulcerative lesions that were observed in the eyes and on the skin of the dogs, guinea pigs, and mice

At present, no animal host has been found by means of the inhalation technics capable of producing the type of pulmonary lesion identical with that of man

Beryllium Metal Fume Study

A small chamber (6 by 6 by 8 inches) was constructed in which groups of rats were exposed to the fumes produced by striking an arc between a carbon electrode and one made of beryllium This chamber was used in the following pilot studies

Fume Concentration

Exposures were regulated by changing the length of time during which he arc was operated, as it was not found possible to regulate the rate at hich the fume was produced by the arc Exposure concentrations main-

tained for periods up to one minute were estimated by means of a filter paper sampler; the concentration obtained during longer exposures could not be measured directly because the increased amount of fume tended to seal the pores of the filter paper and shut off the flow of air through the filter paper sampler. The output of the arc was accordingly determined for a series of one-minute exposures and was *found to give* an approximately constant value of 8.2 mg., plus or minus 0.2 mg., of fume per minute. In the *small exposure unit employed, this yielded a concentration* of 800 mg./m³ and all exposures have been calculated as CT values *(concentration-time, or mg. min./m³) on the basis of 800 CT units* per minute of exposure.

The CT unit, as employed here, is an expression of the concentration of the beryllium metal fume in the small exposure chamber. The value for this unit is found by multiplying the number of milligrams of fume per cubic meter by the number of minutes of exposure. Defining the statement mathematically, it becomes

$$CT = \text{concentration} \times \text{time} = \text{mg. min./m}^3$$

The amount of fume in the chamber at any given time was determined by accurately weighing the quantity of fume collected on a filter paper during a sampling period of one minute. The output of the arc producing the fume was found to give an approximately constant value of 8.2 ± 0.2 milligrams fume per minute. In the small exposure unit employed, this *yielded* a concentration of 800 *mg.*/m³ and all exposures have been calculated at CT values (mg. min./m³) on the basis of 800 CT units per *minute of exposure.*

The exact chemical composition of the fume produced by passing an electric arc between beryllium *metal and carbon electrodes is not* known. It is probable, though, that at the high temperatures employed in the arcing process, the fume is a mixture of beryllium *metal fume,* beryllium nitride, beryllium oxide, and beryllium carbide. Without being able to determine accurately the concentration of each *of these possible* components, the mixture has been called beryllium metal fume.

Acute Mortality.

Five rats were placed in the chamber and exposed to 24,000 CT units (equivalent to thirty minutes of arcing). The total exposure was subdivided into eight exposures of three to four minutes each given at fifteen-

minute intervals so as to avoid excessive temperature rises in the chamber. As a control, 5 rats were exposed in the same manner to a total of thirty minutes of arcing using two carbon electrodes Four of the beryllium-exposed animals died, 2 during the exposure and 2 within one and one-half hours after removal from the chamber, none of the carbon-exposed rats died

Autopsies were performed on the 4 exposed rats which died, and on the 5 control rats The fifth exposed rat which survived the exposure was killed after four days during which time growth appeared normal The results obtained are shown in table XLII

TABLE XLII POSTMORTEM FINDINGS IMMEDIATELY FOLLOWING EXPOSURE TO FUME

Rat No	Cyanosis	Condition of Lung	Lung W / Body W × 100 (per cent)
	A RATS SUCCUMBING TO 24 000 CT UNITS OF BERYLLIUM FUME		
379	Moderate	Hemorrhagic, spotted	0 70
390	Very severe	Very hemorrhagic	2 41
392	Severe	Hemorrhagic	0 96
378	Severe	Hemorrhagic	0 72
		Average	1 20 ± 0 61
	B RATS SURVIVING EXPOSURE TO CARBON ARC		
383	Absent	Pink normal	0 46
384	Absent	Pink normal	0 43
385	Absent	Pink normal	0 50
386	Absent	Pink, normal	0 47
387	Absent	Pink normal	0 51
		Average	0 48 ± 0 03
	C RAT SURVIVING EXPOSURE TO 24 000 CT UNITS OF FUME		
381	Absent	Pink, normal	0 51

It would appear from the above that beryllium fume acts at these levels of exposure as an irritant rather than as a systemic poison The primary cause of death appears to be asphyxia resulting from the destruction of lung tissue or lung function When this destruction is insufficient to cause a lethal asphyxia the animal remains alive and recovers rapidly when the exposure is terminated

To test the above hypothesis three additional groups of 5 rats each were exposed One group was exposed to 24 000 CT units in a single day

tained for periods up to one minute were estimated by means of a filter paper sampler; the concentration obtained during longer exposures could not be measured directly because the increased amount of fume tended to seal the pores of the filter paper and shut off the flow of air through the filter paper sampler. The output of the arc was accordingly determined for a series of one-minute exposures and was found to give an approximately constant value of 8.2 mg., plus or minus 0.2 mg., of fume per minute. In the small exposure unit employed, this yielded a concentration of 800 mg./m³ and all exposures have been calculated as CT values (concentration-time, or mg. min./m³) on the basis of 800 CT units per minute of exposure.

The CT unit, as employed here, is an expression of the concentration of the beryllium metal fume in the small exposure chamber. The value for this unit is found by multiplying the number of milligrams of fume per cubic meter by the number of minutes of exposure. Defining the statement mathematically, it becomes

$$CT = \text{concentration} \times \text{time} = \text{mg. min./m}^3$$

The amount of fume in the chamber at any given time was determined by accurately weighing the quantity of fume collected on a filter paper during a sampling period of one minute. The output of the arc producing the fume was found to give an approximately constant value of 8.2 ± 0.2 milligrams fume per minute. In the small exposure unit employed, this yielded a concentration of 800 mg./m³ and all exposures have been calculated at CT values (mg. min./m³) on the basis of 800 CT units per minute of exposure.

The exact chemical composition of the fume produced by passing an electric arc between beryllium metal and carbon electrodes is not known. It is probable, though, that at the high temperatures employed in the arcing process, the fume is a mixture of beryllium metal fume, beryllium nitride, beryllium oxide, and beryllium carbide. Without being able to determine accurately the concentration of each of these possible components, the mixture has been called beryllium metal fume.

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minute intervals so as to avoid excessive temperature rises in the chamber. As a control, 5 rats were exposed in the same manner to a total of thirty minutes of arcing using two carbon electrodes. Four of the beryllium-exposed animals died, 2 during the exposure and 2 within one and one-half hours after removal from the chamber; none of the carbon-exposed rats died.

Autopsies were performed on the 4 exposed rats which died, and on the 5 control rats. The fifth exposed rat which survived the exposure was killed after four days, during which time growth appeared normal. The results obtained are shown in table XLII.

TABLE XLII. POSTMORTEM FINDINGS IMMEDIATELY FOLLOWING EXPOSURE TO FUME

Rat No.	Cyanosis	Condition of Lung	Lung Wt./Body Wt. ×100 (per cent)
A. RATS SUCCUMBING TO 24,000 CT UNITS OF BERYLLIUM FUME			
379	Moderate	Hemorrhagic, spotted	0.70
380	Very severe	Very hemorrhagic	2.41
382	Severe	Hemorrhagic	0.96
378	Severe	Hemorrhagic	0.72
		Average	1.20±0.61
B. RATS SURVIVING EXPOSURE TO CARBON ARC			
383	Absent	Pink, normal	0.46
384	Absent	Pink, normal	0.43
385	Absent	Pink, normal	0.50
386	Absent	Pink, normal	0.47
387	Absent	Pink, normal	0.51
		Average	0.48±0.0[illegible]
C. RAT SURVIVING EXPOSURE TO 24,000 CT UNITS OF FUME			
381	Absent	Pink, normal	0.51

It would appear from the above that beryllium fume acts at these levels of exposure as an irritant rather than as a systemic poison. The primary cause of death appears to be asphyxia resulting from the destruction of lung tissue or lung function. When this destruction is insufficient to cause a lethal asphyxia, the animal remains alive and recovers rapidly when the exposure is terminated.

To test the above hypothesis, three additional groups of 5 rats each were exposed. One group was exposed to 24,000 CT units in a single day,

as above. Three animals died during the exposure, as compared with 4 dying in the preceding group; the postmortem findings likewise agreed with those shown in table XLII, the lung weights being 1.9, 1.4, and 1.4 per cent of the body weight. Another group of 5 rats was exposed to one half this quantity of fume, or 12,000 CT units; no animals died during

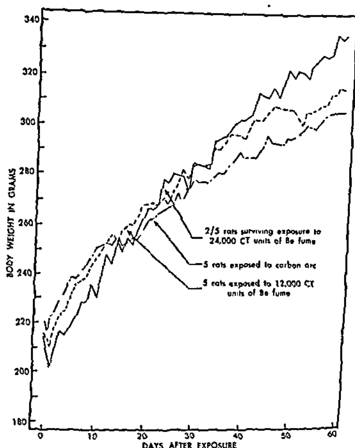


FIG 132 Curves showing growth of rats following a single exposure to beryllium fume

this exposure. The third group was exposed to carbon fumes for thirty minutes, no animals died. The weights of all the survivors were followed for sixty days. The results are shown in fig 132 No reduction in growth rate is demonstrable in any of these curves, even in the case of the two animals surviving exposure at a level approximating an L.D.$_{50}$

As an additional confirmation of the effect of beryllium *fume* on

growth, four groups of 5 rats each were selected whose mean body weights were 50 gm, 150 gm, 200 gm, and 375 gm respectively. Each of these groups was exposed to 12,000 CT units, and daily weights subsequently recorded The results are shown in fig 133, again there is no perceptible after-effect of the exposure visible in the growth

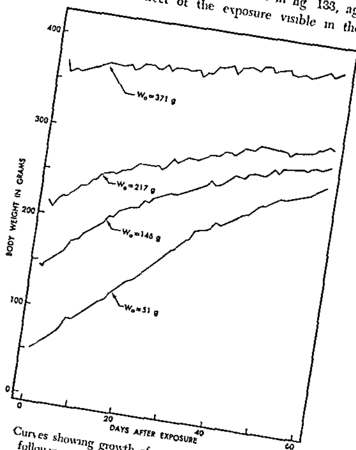


FIG 133 Curves showing growth of rats of four different age groups following a single exposure to beryllium fume

curves At the end of the sixty-day period, autopsies were made on each group with the results given in table XLIII

Effect of Continuous Exposure

Whereas beryllium fume at high levels may act as an irritant, the possibility remains that this effect may serve to mask more specific

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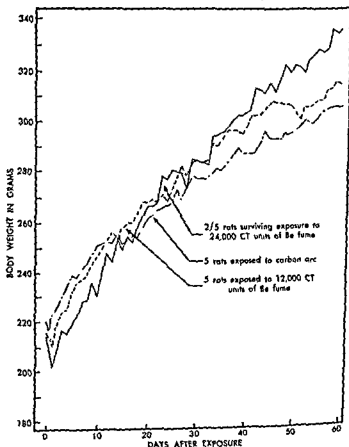


FIG 132. Curves showing growth of rats following a single exposure to beryllium fume

this exposure. The third group was exposed to carbon fumes for thirty minutes; no animals died. The weights of all the survivors were followed for sixty days The results are shown in fig. 132. *No reduction in growth rate is demonstrable in any of these curves, even in the case of the two animals surviving exposure at a level approximating an* L D $_{50}$.

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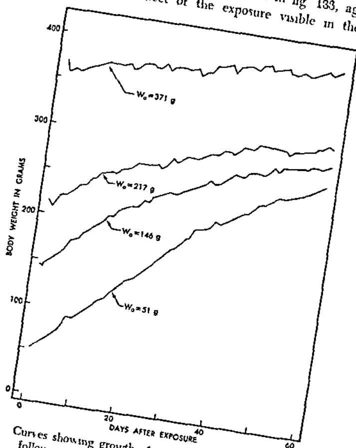


FIG 133 Curves showing growth of rats of four different age groups following a single exposure to beryllium fume

curves At the end of the sixty-day period, autopsies were made on each group with the results given in table XLIII

Effect of Continuous Exposure

Whereas beryllium fume at high levels may act as an irritant, the possibility remains that this effect may serve to mask more specific

TABLE XLIII POSTMORTEM FINDINGS IN RATS 60 DAYS AFTER EXPOSURE TO 12,000 CT UNITS OF BERYLLIUM FUME

Rat group (grams body weight)	*Lungs* Condition	Fractions of group	*Lung wt* / *Body wt.* (per cent)	*Standard Deviation*
150	Pink, normal	5/5	0 58	±0 06
200	Pink, normal	5/5	0 51	0 08
375	Slight hemorrhage	2/5	0 52	0 06
200 (controls)	Pink, normal	5/5	0 50	0 09

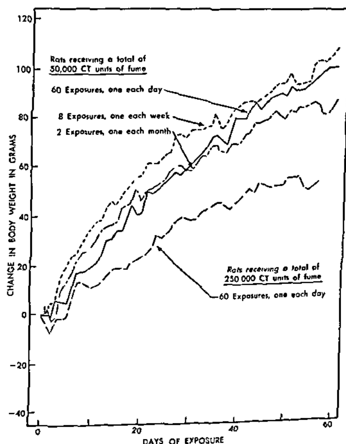


FIG. 134 Curves showing growth of rats during intermittent and continuous exposure to beryllium fume

reactions. In order to test this hypothesis, four groups of 5 rats each were exposed in the following manner The first group received 50,000 CT units given as two exposures of 25,000 units each month, each exposure being distributed over two successive days, to insure the survival of all animals The second group was exposed to 50,000 CT units given

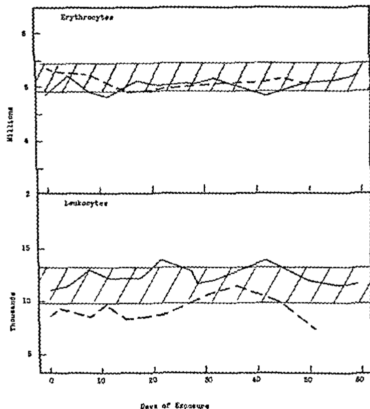


FIG. 135 Changes in count of erythrocytes and of leukocytes in rats during 60-day exposure to beryllium fume

as eight weekly exposures of 6000 units each. The third group received 50,000 CT units given at a rate of 800 units per day for sixty days The fourth group received five times this total dosage, or 250,000 CT units, given as 4000 units per day for sixty days.

None of the animals died during any of the experiments The weight response during the exposure is shown in fig. 134 It will be seen that the

three groups receiving a total of 50,000 CT units each show no evidence of a reduction in growth rate in spite of the fact that this level represents a *total* exposure to fume twice as great as the single exposure which killed four animals out of five.

The fourth group, receiving five times as great an exposure as the

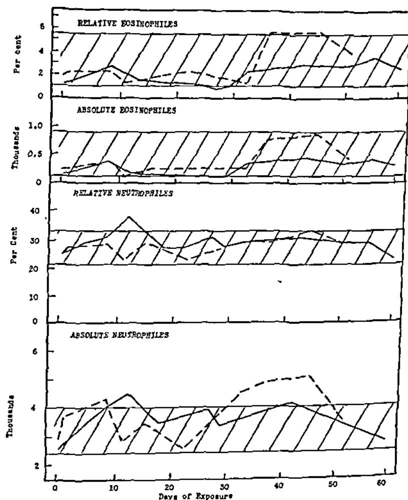


FIG 136 Changes in count of eosinophiles and of neutrophils in rats during 60-day exposure to beryllium fume

first three groups, and 10 times the lethal exposure, shows only a slight reduction in growth rate, increasing in weight by 50 gm while the first three groups increased 90 gm, 100 gm, and 110 gm. respectively.

The hematologic findings for the two groups receiving daily exposures are shown in figs. 135 and 136. It will be seen that while there is a slight tendency toward a progressive eosinophilia and neutrophilia, more marked in the rats that received the greater exposure, the values do not at any time depart widely from the control range.

Autopsies of the animals in each of the groups exposed to 50,000 CT units at the end of the exposure revealed the gross findings shown in table XLIV.

TABLE XLIV POSTMORTEM FINDINGS IN RATS EXPOSED TO 50,000 CT UNITS OF BERYLLIUM FUME

	(Type of damage and fraction of group in which it occurred)							
	Lung		Liver		Kidney		Spleen	
Type of exposure	*Condition*	*Fraction of group*	*Condition*	*Fraction of group*	*Condition*	*Fraction of group*	*Condition*	*Fraction of group*
Daily	Slight hemorrhage	4/5	Normal	5/5	Hemorrhage	2/5	Enlarged	3/5
Weekly	Slight hemorrhage	5/5	Fatty	1/5	Hemorrhage	1/5	Normal	5/5
Monthly	Slight hemorrhage	3/5	Normal	5/5	Petechiae	1/5	Enlarged	2/5

The damage appears to occur chiefly in the lung and to a smaller extent in the kidney. In neither case is the damage so serious as to interfere with normal growth.

Conclusions

The fumes produced by arcing metallic beryllium against a carbon electrode developing high intensities of exposure of 25,000 CT units in a single day appear to act primarily as an irritant. This effect does not appear to be cumulative, for it was found that rats tolerated far greater total exposures as long as no single dose exceeded 12,000 units (equivalent to one hour at 200 mg/m³). Only a slight response, exhibited by a reduced growth rate, was obtained after daily exposure to 4000 CT units per day, equivalent to thirty-three hours at 100 mg/m³.

Summary

Beryllium Sulfate. Data from 56 animals were collected to supply information relevant to the poisonous effects, including the organs in-

jured and the route of the damage, caused *by the inhalation of beryllium* sulfate tetrahydrate dust at a concentration approximating 90 mg. of the salt per cubic meter of air Six criteria of toxicity were utilized in evaluating the information obtained from the animals which comprised 2 dogs, 3 rabbits, 10 rats, 14 guinea pigs, 20 mice, and 7 hamsters The *animals were exposed six hours daily* for a two-week period, a total of sixty-six hours, to a dust of this soluble beryllium salt in a small inhalation exposure chamber

Mortality for all species dying as a result of exposure was 43 *per cent* of the 56 exposed animals or 20 of 20 mice, 2 of 10 rats, and 2 of 7 hamsters. The mice died from the third to the eleventh calendar day with an L D $_{50}$ being attained on the seventh day following the start of exposure No deaths occurred among the dogs, rabbits, or guinea pigs *Weight response* data showed *that all species save the guinea pig were* adversely affected The rabbit lost 5 per cent in weight, whereas the rat and hamster lost 11 per cent *Clinical chemical* values indicated renal impairment and some subsequent regeneration in the rabbits. Much less serious kidney damage and hepatic injury in dogs was indicated from *many chemical tests which included frequent analyses of the blood* for sugar, N.P.N, urea nitrogen, amino acid nitrogen, bromsulfalein, and serum protein All of the urinary variables including amino acid nitrogen/creatinine ratio, sugar, and protein were normal at all times. *Hematologic* results showed definite upward trends in the leukocytic *count, notably the absolute neutrophil counts of the dogs,* rats, and rabbits during the second week of exposure The other cellular blood elements gave no characteristic trend for any of the species External *symptoms* varied somewhat with the species Ocular opacity developed in the guinea pig, mouse, and dog following twelve hours of exposure *Cutaneous lesions of varying size developed over* the body of the dog, while the rats were found to have râles The hamsters and rabbits manifested no external signs of beryllium damage The *histologic findings* showed the effect of absorption of beryllium sulfate tetrahydrate through the respiratory tract of the mouse, rabbit, and rat to be pulmonary damage, *especially edema* This was not the type of injury, however, found in man Additional lung lesions observed included inflammatory exudate in the lumina of the terminal bronchi and *some foci* of atelectasis of the rabbit, hemorrhage of the alveolar sacs of the hamster, and infiltration

of neutrophils and monocytes in the lungs of the rat Hepatic injury was observed in mice dying during the first nine days, but no lesions were noted thereafter, indicating rapid regeneration Renal changes were found in the rabbit and rat but some regeneration of the tubular epithelium was observed in the rabbit kidneys

Marked species variation, but unusually good conformity within each species, was thus observed in the response to the inhalation of $BeSO_4 \cdot 4H_2O$ The sulfate ion, conferring a high acidity upon the molecule as a whole (with an approximate *p*H of 1 0 for the saturated solution), was felt to contribute significantly to the toxicity of the beryllium salt.

Beryllium Metal Fume Rats have been exposed by inhalation to beryllium metal fume at an approximate concentration of 800 mg./m³ of air under a variety of exposure schedules to determine the character of the toxic response. Seven of 10 rats died of pulmonary hemorrhage following exposure to 24,000 CT units of fume administered as eight exposures of from three to four minutes each over a period of two hours When the exposure was one-half this value, or 12,000 CT units, no rats died or showed other untoward response. Moreover, rats were found to tolerate 200,000 CT units or nearly 10 times the lethal dosage if administration of the fume was made at the rate of 4000 units daily for a period of sixty days Some reduction in growth rate, however, was noted on this schedule

It was, therefore, concluded that beryllium metal fume acts as a primary irritant which, when administered rapidly in high dosage, may be fatal but which is tolerated relatively well as long as no single dose exceeds 12,000 CT units No cumulative poisonous effects were seen

Acknowledgment is gratefully made to Dr Harold C Hodge, Head of the Division of Pharmacology, Atomic Energy Project, and Professor of Pharmacology, School of Medicine and Dentistry, University of Rochester, for his helpful assistance and guidance in these studies

Discussion

HERBERT E. STOKINGER, PH D.*

It is unique in this symposium, at least, to discuss one's own paper, but I feel that after listening to some of the discussions of clinical and

* Head, Industrial Hygiene Section, Division of Pharmacology, Atomic Energy Project, University of Rochester, Rochester, New York

jured and the route of the damage, caused by the *inhalation of beryllium sulfate tetrahydrate dust* at a concentration approximating 90 mg. of the salt per cubic meter of air. Six criteria of toxicity were utilized in evaluating the information obtained from the animals which comprised 2 dogs, 3 rabbits, 10 rats, 14 guinea pigs, 20 mice, and 7 hamsters. The animals were exposed six hours daily for a two-week period, a total of sixty-six hours, to a dust of this soluble beryllium salt in a small inhalation exposure chamber

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* Head, Industrial Hygiene Section, Division of Pharmacology, Atomic Energy Project, University of Rochester, Rochester, New York

experimental work in beryllium poisoning, it would not be amiss to state precisely what our experimental approach is at Rochester.

We have been assigned by the Atomic Energy Commission the task of learning what we could about the toxicology of beryllium as it enters into the fabrication of beryllium metal. Now that, you see, excludes largely what has been said about the beryllium lamp industry. In the fabrication of the metal, we are concerned only with the metal itself and the products that are necessarily involved in its production. This you have heard this morning.

In this work we have been attempting to open up new experimental approaches to the chemistry of these materials as they are related to their biochemical action in the body. This we hope we can present at some later date.

We have also been assigned the task of determining the toxic limits of the various compounds of industrial importance in the manufacture of beryllium, a number of which have already been mentioned by various groups. These have been explored by the intratracheal route and, as described in this last paper, by inhalation.

We are also interested in determining the toxic effects of these materials, and we are engaged, in a preliminary way, in developing methods of detection of the action of these materials in the body in the hope that we can open up a new clinical approach, which has also been started in Chicago.

And lastly, if we can, we would like to get some methods of prophylaxis, possibly through some more precise knowledge of the mode of action of beryllium, for which we also have programs under way, especially from the enzymic standpoint.

Listening to this last paper, it occurred to me that there might be two points of general interest for consideration. Up to the time of this meeting, at least, I think that there has been some hesitation among individuals to state that beryllium is the causative agent. I think we can say here that we can certainly produce a poisonous response from beryllium compounds, we have shown this with pure beryllium alone, and in this inhalation study it was done with dispatch We know the effect of a few days of exposure in a number of the species and of at least two weeks' exposure in others Moreover, there were considerable similarities in the response of the animals, to that seen in man. Because of the

intensity of the exposures, the lesions were exaggerated in the lung and there was spreading of the injury into other organs such as the kidney and the liver.

And that brings me to the second point that I think is significant. There has been considerable controversy at this meeting about the action of beryllium Is its action systemic or local? It seems to me that this experiment could offer a reconciliation of these two opposite views that have been presented if one assumes merely that these effects of systemic reaction are the response to an overwhelming injury to an organ which has a secondary effect in another I should think that would be a reasonable interpretation, and the controversy, it seems to me, is but "a tempest in a tea-pot."

Further Discussion

MR MERRILL I would like to raise the question as to the activity of these compounds. It seems to me that it has been pointed out at various times during the speeches and discussions that, first of all, the fluoride was very active and cases were found to occur within a very short period of time after exposure to fluorides

Similarly for the beryllium compounds, the sulfate took a longer period to show an effect, and with beryllium oxides and silicates, there apparently developed a still longer period of onset, causing the so-called chronic disease

It seems to me that those are phases which Dr. Hodge and Mr Maynard brought out this morning, showing the different compounds and their effects, and particularly were they able to show that the soluble compounds were quite active and the insoluble compounds less so, especially the metal and the oxide, whereas the carbonate in one case showed a marked effect on growth

In particular, I would like to make the point that beryllium oxide can be very active or inactive, depending upon the state of calcination When heated to about 1400° C, beryllium oxide can be relatively inactive in relation to material calcined at 1000° C

I would like to suggest the possibility that an oxide formed at a temperature nearer to room temperature can be far more active chemically than those just mentioned In these cases from a foundry where there

was apparently no exposure to people who were close to the pouring of the metal, but apparently exposure did occur to people at some distance, there may be a definite change in the type of material to which the individual is exposed. Maybe those close to the foundry are exposed only to the metal, but those far away are exposed to an oxide of the metal, and by the same token, I point out that maybe that oxide, if it so formed, could be very active, because it would be formed at a relatively low temperature and not subject to high temperature calcination. Possibly this is one of the reasons that no cases have been directly traced to exposure to beryllium oxide, due to the fact that in most cases where a person could be exposed to the beryllium oxide, the oxide exists in a relatively inactive state

DR HODGE· I would just like to stress one point You who are used to expressing concentration in milligrams per liter, please note that the concentrations of the beryllium fume here were in milligrams per cubic meter, since there are one thousand liters in a cubic meter, a factor of one thousand is involved

DR HOWLAND. One thing I think ought to be clarified for those of you who are not familiar with methods of animal exposure. This concentration is determined for the air the animal is breathing, but does not represent the concentration the animal takes into his body. That is one of the most difficult experimental things to do the determination of about how much toxic material it requires to cause all this trouble. We have been working on it for two years and I don't know whether we have the answer. Particle size and concentration, settling, absorption, and solubility all enter into it For example, soluble material never reaches the alveolar spaces at all, being dissolved along the mucous membranes on the way down

DR VORWALD· That is why our primary effort here has always been on the inhalation studies, supplementing those studies by the other methods. intratracheal, intraperitoneal and intravenous injections Our crucial experiment involves inhalation of the dust from the atmosphere, thus there is no unnatural interference with the entrance of the dust into the lung.

MR. DELAHANT. Would it be possible to collect some of those fumes and make studies by means of X-ray diffraction?

MR LASKIN· We have collected them, and although it is possible to

make these studies, the field of electron diffraction is more promising This field is, however, so new that we are still at the stage of learning to interpret the results

DR HOWLAND And also electron-microscope studies have been worked out

CHAPTER 22

A Review of Analytical Methods for Beryllium

WILLIAM F. NEUMAN, PH.D.*

In this review, analytical procedures for beryllium are to be considered, *with emphasis* on the analysis of biologic specimens In dealing with biologic materials, there are a number of limitations which have to be considered before any analytical procedure can be critically evaluated

In the first place, the L D $_{50}$ is important in determining the sensitivity *required* of any analytical procedure. Beryllium administered intravenously is very toxic; the L D $_{50}$ is approximately 0 36 mg./kg Thus, for distribution and excretion experiments, not more than 0 2 mg /kg. can be administered. At such a dose level, many tissues may be expected to contain 0 1 microgram per gram or less Thus any procedure to be useful must detect with accuracy quantities much less than one microgram

Secondly, since there are a host of other elements present in any biologic sample, the method must be highly specific and not subject to interference by relatively large proportions of similar and dissimilar elements.

Thirdly, since the high toxicity of beryllium requires that ultra-microtechnics be applied, rigorous precautions must be exercised in all phases of the study to insure against possible contamination.

Preparation of Samples

One of the technical difficulties attending the analysis of beryllium samples is the volatility of the chloride of beryllium No conceivable chemical method can be expected to give reliable results unless all organic matter is first removed. In our experience, temperatures as high as 600° C are required to give complete ashing of most tissues Beryllium chloride boils at temperatures over 400° C. Since all tissues contain fair

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amounts of chloride, varying quantities of beryllium will be lost in ashing. Urine is particularly troublesome in this respect.

Two alternative schemes for ashing are available. Samples may be wet-ashed in sulfuric acid (Kjeldahl procedure), in this method all chlorides are distilled off before the temperature rises above the boiling point of beryllium chloride. Although this procedure has not, as yet, been tested in our laboratory, no technical difficulties are to be anticipated. In general, wet-ashing technics are tedious. Accordingly, a procedure developed in our laboratory offers some advantages. The sample is placed in a platinum crucible together with 2 gm of sodium pyrophosphate, and placed in a muffle furnace. The temperature is raised slowly and left at 400° C until all carbonaceous material is burned off. The samples can be dissolved with the aid of heat in small volumes of 2N HCl.

Analytical Methods

Two chemical, one fluorescent, and the spectrographic methods for determining beryllium have been studied.

Colorimetric Methods. The method of Fairhall[12] was studied in detail.[140] Several difficulties were encountered with the procedure as reported by Fairhall. The beryllium sample was mixed with 1,4 dihydroxy anthraquinone, 2 sulfonic acid in ammonium acetate buffer at approximately pH 7.0. A red color is produced in contrast to the yellow blank. It was found that pH control was critical and, since it is a well-known fact that the ammonium acetate does not buffer at pH 7.0, histidine hydrochloride was substituted. Heating appeared to be necessary for full color development. Spectrophotometric analysis of the color of the blank and of a beryllium sample showed that maximum sensitivity is obtained if light of a wave length of 575 millimicrons is employed. The limit of detection is of the order of 0.5 micrograms. The standard error is 12 per cent. Many substances interfere, among which are F, Fe, PO_4, and Al.

Another procedure,[117] developed in our laboratory, utilizes aluminon (aurin tricarboxylic acid) as a color reagent. Dr Rothstein had noticed that beryllium interfered in the determination of aluminon. Further study showed that this reaction could serve as a method with some advantages and some disadvantages, as compared with the Fairhall procedure. Beryllium is mixed with aluminon at pH 7.5 in ammonium

chloride buffer. The color produced is read against light of 535 millimicrons wave length The limit of detection is 1 microgram. The standard error is about 10 per cent, and again many substances interefere, particularly Fe, Al, Pb, Ca, Cu, and Mn. PO_4 and F when present in excess (10 or 100 to 1 moles) also interfere.

Fluorescent Method Fairhall[12] *also reported a fluorescent procedure* for the analysis of beryllium samples Again, it was difficult to duplicate Fairhall's reported results[624] *Variations in the ratio of dye to beryllium* and *pH* were observed to have pronounced effect on the fluorescence produced by a given quantity of beryllium. Beryllium was mixed with 1 amino, 4 hydroxy anthraquinone in diethyl amine buffer at *pH* 11 3 The fluorescence was read on a sensitive fluorometer built in our laboratory. The limit of detection is about 0 5 micrograms. The standard error is about 12 per cent and again many substances interfere, principally Ca, *Mg, Fe,* Cu, and *Mn No problem was offered by PO_4, F,* and *other* common anions—an advantage of this method.

Spectroscopic Method. *Dr Steadman*[780] *has investigated the spectro*graphic method for beryllium analysis As might be expected, beryllium, having a simple emission spectrum, is an element which is particularly suited to spectrographic analysis Without the need of special sensitizers, very high sensitivity can be attained Employing fairly standard technics —a commercial Bausch and Lomb spectrograph, DC carbon arc with either platinum or iridium as an internal standard—as little as 0.005 microgram can be *detected (2348 Å) By shifting to another* line (2494 Å) greater amounts can be quantitated, up to 10 micrograms. The *greatest drawback is the error,* which *for a single* determination probably is of the order of 25 per cent No chemical separation is necessary since beryllium distils with difficulty and other elements do not materially interfere

Radio-isotopes

There are two radioactive isotopes of beryllium which might be useful Be^{10} and Be^7 The principal difficulty in the use of both of these is that of obtaining samples of sufficient activity Beryllium has a small "cross section" and therefore requires long bombardment time For our purposes, Be^7 was more useful This isotope is produced *principally by the* bombardment of lithium by protons. Since it is a transmutation reaction,

pure isotopic beryllium is obtained and the sample may be diluted with inert carrier beryllium to give the desired specific activity This isotope—Be^7—is a gamma emitter Although no gamma-counting tubes are commercially available, almost any type of Geiger-Mueller tube will register gamma radiation In our laboratory, the immersion type designed by Bale proved to be more efficient than the popular mica-window type of tube.

In brief, the essential details of the radioactive technic of studying beryllium are as follows:

1 A lithium target is bombarded with a proton beam for about six hours in the University of Rochester cyclotron
2 The sample is dissolved in 0 5N HCl, diluted, boiled, and filtered, Then 0 1 to 10 mg of beryllium carrier is added, plus 10 mg of zinc The solution is made alkaline with ammonia at the boiling point. The precipitate which forms is filtered and washed with ammonia The sample is reprecipitated without zinc, washed, dissolved in dilute HCl, and neutralized to pH 4 or 5 The salt concentration is adjusted to 0 9 per cent
3 Generally one obtains for injection purposes 50 cc containing 250,000 c/m
4 A minimum of 50,000 c/m are administered to the experimental animal
5 Tissues are excised, dry-ashed, dissolved in 2N HCl, and counted

Only preliminary distribution data were available in time for clearance, therefore, we are unable to discuss further the application of this technic

Summary

Procedures for the analysis of biologic specimens for their beryllium content are discussed Two colorimetric, one fluorescent, and the spectrographic methods are presented, together with data on the accuracy, sensitivity, and specificity of each

The advantages of, and experimental procedures for, the use of beryllium isotopes are also reviewed

Discussion

THOMAS M. DURKAN*

The determination of minute quantities of beryllium in biologic material has always been a difficult problem and Dr. Neuman's contribution to the subject is a very useful one. When tissue from the first Salem and the Cleveland cases was received at the Saranac Laboratory about four years ago, we were not in a position to test carefully the analytical procedures for beryllium suitable for microgram amounts. Several chemical methods were described in U. S. Public Health Bulletin 181 but it was stated that none was entirely satisfactory and that correction graphs must be developed from samples containing known amounts of beryllium We therefore relied more on the spectrographic determinations of beryllium which were made for us by several different laboratories. Mr. Poritsky of the General Electric Company, who presents a paper† in this symposium, has carried out many spectrographic analyses for us In at least two of the cases, beryllium was determined chemically by Dr. Fairhall.

It is interesting to note that Dr. Neuman found the analytical methods adequate for his particular survey problem but not satisfactory for unrestricted use in biologic studies We still need a fairly universal chemical method that can be applied to all kinds of biologic material and will yield reliable values Within the past year Dr. Klemperer has set up a biochemical laboratory at Trudeau to study this problem and attempt to work out a better analytical procedure The method must be very sensitive since Dr. Neuman has estimated that it should be capable of detecting as little as 0.5 microgram of beryllium It should also be adapted to a wide range of beryllium concentrations. Thus the amount of beryllium per gram of tissue in the first case of the Saranac Laboratory series was 0.06 microgram, in the second case, 4 micrograms, in the third case, 33 micrograms. These three values encompass a range of more than 500 to 1.

Dr. Neuman pointed out that the common practice of eliminating the organic portion of biologic material by ashing the specimen in a muffle

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† See Chapter 27. (*Ed*)

furnace may volatilize beryllium as the chloride unless provision is made to fix it as a stable salt, such as the phosphate. It is often overlooked that dry ashing even at the comparatively low temperature of 500° C may lead to the loss or alteration of inorganic components of biologic specimens Mr Donald Bailey of this laboratory has found that the crystallographic structure of such a stable mineral as quartz may be destroyed by dry ashing when an excessive amount of alkali salts is present in the specimen.

The disclosure by Dr Neuman that there are two radioactive isotopes of beryllium emitting gamma radiation that can be traced with a Geiger counter offers great possibilities in studying the distribution of beryllium in the experimental animal Perhaps greater attention should be directed to the use of tracer technics in the beryllium investigation

In conclusion I should like to ask, first, are these radioactive isotopes available for our use, and second, will the method which Dr Neuman has outlined be published in any technical journal in the future? Also, how did he reprecipitate the beryllium without the zinc?

Further Discussion

DR. NEUMAN. I will answer the last one first Again with ammonia and in this case you use a very retentive filter paper and you won't lose much beryllium We always add 10 mg of inert beryllium as a carrier since obviously, if we were trying to precipitate a tenth of a microgram of the isotope, we would not be very successful

I will refer both the first and the second question to the representative of the Atomic Energy Commission, Dr Howland

DR HOWLAND· We are very fortunate in having with us today a representative of the Isotopes Branch of the Atomic Energy Commission who, I am sure, would be glad to comment on these questions Dr Albert H. Holland

DR HOLLAND With regard to the production of beryllium isotopes, there are two separate problems involved, as you have heard Dr Neuman indicate Of course, Mr Durkan is most anxious, as most investigators are, to obtain this material and get started on some of these problems The 43-day isotope Be^7 can only be produced by cyclotron bombardment It

is notoriously expensive to obtain and, proportionately, the yield of active material is quite small Those interested in acquiring further information may do so by contacting the U. S. Atomic Energy Commission, Isotopes Division, P. O. Box E, Oak Ridge, Tennessee.

The other beryllium isotope, Be^{10}, has not gone into production at Clinton National Laboratories, which is the manufacturing pile for the isotope distribution program. It is unlikely that this isotope will ever be available for investigational use, since it has a half-life of the order of 10,000 years.

It should be pointed out that, once you have placed an order for Be^7, your problems are really just beginning, as Dr. Neuman has previously implied This isotope is a gamma emitter and requires the practice of considerable personnel protection precautions, as well as rather expensive radiation measuring and monitoring equipment in order to attain safe working conditions

DR. HOWLAND The next question, when will Dr. Neuman's paper be published? That is difficult to answer If it has nothing patentable in it, if it is not immediately useful, we could have it out in short order. People have the idea that, to get papers out for clearance is a difficult thing Actually, it's a fast thing. It depends on having enough initiative and enough nerve to go ahead. I think Dr Hodge can vouch for that. That answers the three questions

I think it would be an excellent idea to call on Dr. Klemperer for a few comments.

DR KLEMPERER I am glad I can bring out the difficulties in determining beryllium We have heard in the last few days about analytical determination of beryllium which had been carried to the third decimal. Such data, I believe, have to be taken with a gram of salt.

First, if any data are published, they cannot be interpreted unless the method is published in detail. Second, in order to evaluate analytical data, we should know the recovery of beryllium added to the unknown Beryllium is a substance which is notoriously hard to handle. It has a tendency not to precipitate when it is alone, and then to coprecipitate with everything else.

I'm certainly looking forward to Dr. Neuman's new method and hope that all the difficulties will be solved

Another point which I want to bring up probably is known to all of you, but perhaps is not sufficiently appreciated When we hear of one microgram of beryllium, we should not forget its low molecular weight One microgram of beryllium, biologically speaking is more than twenty times the amount of one microgram of lead

DR DUTRA I believe I ought to say something about the three-decimal-place estimations of beryllium, because they all came out of our laboratories The chemist, Mr Cholak, who developed the method, which incidentally has been submitted for publication and remodified slightly since then, will be here tomorrow and will discuss it in detail Any questions or remarks on the subject can be directed to him at that time.

DR AGATE I would like to ask Dr Neuman whether his methods, new or old, are applicable to bone New chemical methods are being evolved in England which, though not applicable to bone, are applicable to all other tissues

DR NEUMAN I hope the method will be good Dealing with pure solutions, it is The part of my manuscript which was deleted for security reasons dealt with the isolation of beryllium I cannot vouch for the errors or accuracies of the particular procedure, which was developed at another laboratory I can say this much, that *our* emphasis to date has been to develop a method that is good to 5 per cent, then we can study isolation procedures I don't know whether or not the extraction procedure I would like to have told about could be used on bone, but I think it should be applicable Obviously, precipitation methods are very dangerous when applied to the small quantities of material present in biologic specimens

CHAPTER 23

An Analysis of Dust and Fume Hazards in a Beryllium Plant*

SIDNEY LASKIN, ROBERT A. N. TURNER,† AND HERBERT E. STOKINGER, PH.D.‡

In the fall of 1946, an invitation was extended to the industrial hygiene group at Rochester to visit a beryllium plant among whose personnel definite histories of beryllium poisoning were known. A survey of this plant (designated as Plant B) was therefore made with the primary purpose of providing information which would serve as a basis for toxicologic investigations of beryllium at Rochester. This survey included an examination of the plant operations, the medical history, types of beryllium poisoning characteristic of the plant personnel, and a survey of the plant environment This report is a summary of the results obtained and is divided into two parts. The first is a review of the plant operations and its medical history These are presented for the purpose of characterizing the types of beryllium poisoning and in order to indicate the major beryllium compounds involved in the reported case histories The results reported are based upon records of the company health department and reports of the company physician and the district resident safety engineer, Mr. R A. N Turner The second part of this report presents an analysis of the plant environment in terms of atmospheric dust concentrations, dust particle sizes, and types of substances involved in various operations, and are the results of the survey made by the Rochester group at Plant B

* Acknowledgment is gratefully made to Dr Harold C Hodge, Head of the Division of Pharmacology, Atomic Energy Project, and Professor of Pharmacology, School of Medicine and Dentistry, University of Rochester for his assistance and guidance in these studies

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TABLE XLV PROCESSES AND POTENTIAL HAZARDS IN THE PRODUCTION OF BERYLLIUM METAL AND ITS COMPOUNDS

Process	*Beryllium compounds*	*Other compounds added*	*Major potential hazards*	*Health history*
Ore melting	Raw beryl ore $3BeO \cdot Al_2O_3 \cdot 6SiO_2$		Ore dust SiO_2 fumes	1 hospital case of long duration (?)
Ore treatment	Processed ore $BeSO_4 \cdot 4H_2O$	H_2SO_4	Processed ore dust Acid mists and fumes ($BeSO_4$)	1 fatal case
Crystallizing	$BeSO_4 \cdot 4H_2O$	$(NH_4)_2SO_4$	Acid mists and fumes ($BeSO_4$)	Numerous respiratory and dermatitis cases
Beryllium oxide production	BeO	$(NH_4)_2S$	Fumes of PbS, CuS, SO_2 Dusts of BeO	Very minor dermatitis (inspectors)
Beryllium copper production	BeO BeCu	Cu, carbon	BeO, Cu, and BeCu Dusts and fumes	6 respiratory cases 3 fatal (?)
Beryllium metal production	BeO $(NH_4)_2BeF_4$ BeF_2 Be metal	Acid fluoride $(NH_4)_2S$	Acid fluoride $(NH_4)_2BeF_4$ mists Fumes and dusts of $(NH_4)_2BeF_4$, BeF_2, HF, NH_4F, Be metal, BeO	Serious dermatitis Many respiratory cases

workers, therefore, has been used in Plant B as a rough barometer of individual susceptibility to respiratory tract involvement.

The second type of skin manifestation, the beryllium ulcer, occurred in the same operations as those responsible for the dermatitis cases. The prerequisite for this condition appeared to be a small abrasion of the skin into which small crystals of beryllium fluoride or sulfate became embedded. There was a tendency of the surface layer of the skin to heal over the embedded crystal and form a small indurated papule. The papule underwent necrosis and finally formed a small abscess superficially apparent by a surrounding area of erythema.

Microscopically, the ulcer showed typical tissue reactions to a foreign body with a definite increase of the surrounding epithelial layers and an increase in the numbers of fibroblasts surrounding the ulcer. In most instances, a definite crystal fragment could be identified.

The ulcer occurred on exposed parts, particularly the forearm and hands, was discrete, and as a rule, single. It caused little distress unless infected or located near a joint. If neglected, the lesion persisted until traumatic extrusion of the inclusion center occurred. Healing did not occur until the crystal was removed by incision of the papule and curettage of the fibrous base of the ulcer.

Respiratory tract manifestations were classified in the case histories according to the regions of the respiratory system involved. These include chemical nasopharyngitis, chemical tracheitis, chemical bronchitis, and chemical pneumonitis. For purposes of this discussion, the tracheitis and bronchitis cases are collectively grouped as tracheobronchitis.

Chemical nasopharyngitis occurred principally among tenders of furnaces where beryllium sulfate was ignited to produce beryllium oxide and where beryllium fluoride was used in the production of pure beryllium metal.

The irritation of the nasal and pharyngeal mucous membranes varied in degree and was frequently associated with a dermatitis of the face. The chief complaint was soreness of the nose and throat associated with mild epistaxis, manifested by blood clots being blown from the nose. As a rule, cough was not present. There was a diffuse swelling of the mucous membranes with a considerable hyperemia. Epistaxis was secondary to vascular enlargement in the nasal mucosa. In some untreated cases, fissures occurred and persisted for two months. The patients were afebrile and chest and laboratory findings were negative.

Chemical tracheobronchitis occurred from the same operations as the nasopharyngitis cases It was characterized by cough, râles in both lungs, but by normal serial roentgenograms The commonest complaint was the cough, nonproductive except for occasional blood-streaked mucoid sputum Symptoms of nasopharyngitis were usually concurrent, and in addition some patients showed mild dyspnea, anorexia, and weight loss. Râles, characteristically present in the early phase of inspiration over the lower lung fields, were fine early in the disease, later becoming coarse Vital capacity was reduced There was an occasional low-grade fever, associated chill, however, never occurred. Complete rest was required for recovery Continued work during this illness proved dangerous in either delaying recovery, or in a subsequent development of true pneumonitis

Chemical pneumonitis represented the severest form of beryllium poisoning It developed in workers on many different jobs under varying conditions No single operation could be generally isolated as the source of exposure Four deaths were reported in 1943, on which case histories are available for 3 The findings showed that the pneumonitis progressed either to complete recovery or to death Typical symptoms were cough with occasional blood-streaked sputum, substernal burning pain, shortness of breath, cyanosis in most cases, abnormal taste, anorexia with some weight loss, and increasing fatigue The dominant physical findings were rapid pulse, râles in both lungs, and a reduced vital capacity Signs of infection were conspicuously absent The temperature was not greatly elevated except in the terminal states of the fatal cases Erythrocyte sedimentation rate was essentially normal Blood counts and chemical findings were also generally normal

Roentgenologic changes in the lung fields did not usually appear until two or three weeks after the onset of symptoms and physical signs Changes were bilateral and diffuse in all cases and varied with the severity of the disease In order of appearance the changes were. (1) diffuse haziness of both lungs, (2) development of soft irregular areas of infiltration with prominence of peribronchial markings In the terminal cases, further signs of consolidation appeared In those cases which recovered, there was an absorption of the soft infiltration and the appearance of discrete conglomerate nodules scattered throughout both lung fields This was followed by clearing of the lung fields after from one to three months. As a rule clearing of the lungs on roentgenologic examina-

TABLE XLVI HISTORY* OF BERYLLIUM POISONING AT PLANT B

Predominant compound	Manifestations of beryllium poisoning	Year	No. of cases: Total	Sex: M	Sex: F	Range of ages (Years)	Range of Service	Range of time lost (Days)
Beryllium sulfate	Dermatologic	1943	8	6	2	16–58	2–12 days	2–20
		1944	6	5	1	21–45	3–14 days	6–25
		1945	8	8	0	24–64	4–14 days	5–19
		1946	4	2	2	27–35	12–42 days	7–19
Beryllium sulfate	Respiratory	1943	22	14	8	18–66	4 day–6½ yr.	2–120 and 1 fatal
		1944	6	3	3	19–45	10 day–1½ yr.	4–91
		1945	8	8	0	33–54	1 mo.–3 yr.	8–90
		1946	0	0	0			
Beryllium fluoride	Dermatologic	1943	5	3	2	17–41	8–42 days	3–27
		1944	2	2	0	17–61	9 days–6½ mo.	6
		1945	16	15	1	21–55	6–77 days	5–32
		1946	19	19	0	18–56	6–61 days	0–20

Beryllium fluoride	Respiratory	1943	6	6	0	24–41	7 days–14 yr	3–103
		1944	1	1	0	47	34 days	150
		1945	9	9	0	21–65	3 wk –3½ yr	8–60
		1946	7	7	0	22–29?	9 days–14 yr	7–19
Beryllium copper alloy	Dermatologic	1943 to 1946	0	0	0			
Beryllium copper alloy	Respiratory	1943	4	4	0	18–48	1–10 mo	4–20 and 2 fatal?
		1944	2	2	0	41–47	2 mo –7½ yr.	15–124
		1945	0	0	0			
		1946	0	0	0			
Beryllium metal	Dermatologic	1943 to 1946	0	0	0			
Beryllium metal	Respiratory	1943	0	0	0			
		1944	0	0	0			
		1945	0	0	0			
		1946	3	3	0	25–29	5 wk –5½ yr.	6–14

* Based on available records of Plant B Health Department

TABLE XLVII CASE FREQUENCIES OF BERYLLIUM POISONING IN PLANT B

Year	No cases			Av no cases per month			Av no employees per month			Av monthly exposure (man-hours)	Case frequency (% employees)			Case frequences 10⁶ exposure hr. total yearly cases
	Total	Sex		Total	Sex		Total	Sex			Total	Sex		
		M	F		M	F		M	F			M	F	
1943	45	33	12	3 75	2 75	1 00	151	126	25	28,276 9	2.48	2 18	4 00	132 6
1944	17	13	4	1 42	1.08	0 33	119	89	30	22,352.7	1 19	1 21	1.10	63 5
1945	41	40	1	3 42	3 33	0 08	113	89	24	19,792.3	3 03	3.74	0 33	172 8
1946	33	31	2	2.75	2 58	0 17	68*	54*	14*	11,548 5*	4 04	4 78	1 21	238.1

*Based on 11 month period (January-November)

tion occurred before complete subsidence of symptoms or disappearance of all physical signs

Necropsies on several cases showed a typical pneumonitis. The pathologic findings were similar. Significant changes were found only in the lungs The tissue sections showed large numbers of plasma cells, the relative absence of polymorphonuclear infiltration, diffuse pulmonary edema, and hemorrhage Fibroblasts with evidence of organization were present, although no fibrosis was found on roentgenologic examination of recovered patients

TABLE XLVIII PERCENTAGE CASE FREQUENCIES OF BERYLLIUM POISONING IN TERMS OF THE PRINCIPAL OCCUPATIONAL DISEASE MANIFESTATIONS

	Dermatologic			*Respiratory*		
Year	*Total no cases*	*Av no cases per month*	*Case frequency in % employees*	*Total no cases*	*Av no cases per month*	*Case frequency in % employees*
1943	13	1 08	0 72	32	2 67	1 77
1944	8	0 67	0 56	9	0 75	0 63
1945	24	2 00	1 77	17	1 42	1 26
1946	23	1 92	2 82	10	0 83	1.22

Table XLVI shows the history of beryllium poisoning at Plant B as correlated with the principal compounds involved in the respiratory and dermatologic disorders. Tables XLVII, XLVIII, and XLIX present an analysis of the plant medical records showing the relation of the compounds to the case frequencies. This analysis cannot be considered entirely accurate because the available records were incomplete with respect to individual occupations, the total number and sex of the personnel exposed and time-production data for each of the operations. In addition, several of the case histories represented recurrences. The analysis, therefore, is presented as a guide in describing the extent of the beryllium hazard at the plant

In table XLVI four beryllium materials compose the list of substances implicated in the entire number of 136 reported cases: beryllium sulfate, beryllium fluoride, beryllium metal, and the beryllium-copper alloy During the four-year period reported, case histories of respiratory tract manifestations were imputed to all four substances. To only the sulfate

Table XLIX CORRELATION OF CASE FREQUENCIES OF BERYLLIUM POISONING WITH BERYLLIUM COMPOUNDS

Compound	Year	Total no cases		Dermatologic		Respiratory	
		Av no cases per month	*Case frequency (% employees)*	*Av no cases per month*	*Case frequency (% employees)*	*Av no cases per month*	*Case frequency (% employees)*
Beryllium sulfate	1943	2.50	1.66	0.67	0.44	1.83	1.22
	1944	1.00	0.84	0.50	0.42	0.50	0.42
	1945	1.33	1.18	0.67	0.59	0.67	0.59
	1946	0.33	0.49	0.33	0.49	0.00	0.00
Beryllium fluoride	1943	0.92	0.61	0.42	0.28	0.50	0.33
	1944	0.25	0.21	0.17	0.14	0.08	0.07
	1945	2.08	1.84	1.33	1.18	0.75	0.67
	1946	2.17	3.19	1.58	2.32	0.58	0.86
Beryllium metal	1946	0.25	0.37	0.00	0.00	0.25	0.37
BeCu alloy	1943	0.33	0.22	0.00	0.00	0.33	0.22
	1944	0.17	0.14	0.00	0.00	0.17	0.14

and fluoride operations, however, were ascribed cases with both respiratory tract and dermatologic manifestations

The general plant history shows 45 cases for 1943, a large number for a plant this size, during which time 3 reported respiratory fatalities occurred (1 in sulfate and 2 in beryllium copper production) Although a definite decrease is shown for 1944 with only 17 cases reported, the incidence apparently returned to the 1943 level in 1945 and 1946 with 41 and 33 cases reported respectively During this period, enclosures of various operations (particularly the sulfate) were made by the plant management The effects of these and an increased medical vigilance by the company health department are reflected in the absence of cases in the beryllium-copper production after 1944 and in the decrease of respiratory cases in the sulfate operations Beryllium fluoride cases, however, accompanying an increase in production, showed a definite increase reaching the proportions of 26 out of 36 reported cases in 1946 The cases attributed to beryllium metal appear only in 1946 (see table XLIX) The severity of the disease in individual cases decreased during the reported period This is indicated by the relative ranges of time lost given in table XLVI

The range of ages of the workers, also shown in table XLVI, appeared to be usual for this type of industrial worker, with a range of between 20 and 50 years The periods of service show that the average exposure for the acute respiratory manifestations were from one to four months. Several of the respiratory cases showed manifestations as early as from three to ten days after exposure, indicating possible allergic responses The dermatologic responses appeared within an average exposure period of from seven to ten days with the earliest reported cases appearing in from two to three days

Sex differences between the case histories and types of manifestations could not be completely analyzed because records of the number of males and females engaged in each operation were not available Incomplete records on case histories also prevented an analysis in terms of specific occupations The types of occupations listed among the case histories include diverse categories as process operators, furnace tenders, machinists, foremen, construction workers, maintenance help, and electricians

Table XLVII, showing the case frequencies of beryllium poisoning

annually at the plant, also presents a partial analysis with respect to sex The results are given in terms of percentage frequencies and in terms of the rate per million hours of exposure. Since the plant had an exceptionally high labor turnover, the total number of individuals exposed could not be determined All frequencies are, therefore, based upon average total monthly numbers of employees and total man-hours of exposure determined from payroll records

For the entire four-year period of the 136 reported cases of beryllium poisoning, 117 (86 per cent) were males and 19 (14 per cent) were females. The average number of employees during this period was 112.8 per month of which 79.3 per cent were males and 20.7 per cent were females Examination of the yearly record in table XLVII shows that, although the above figures indicate no significant difference between the sexes, the female percentage frequency rate was approximately twice that of the male in 1943. For the periods from 1944 through 1946, the male percentage frequency rates were significantly higher than those of the female Further study of the 1943 cases indicates the higher female rate to be primarily among sulfate employees showing respiratory manifestations.

During the period studied, the average monthly number of employees shows a definite decrease from 151 in 1943 to 68 in 1946 Corresponding with these values was an almost identical decrease in monthly exposure hours of from 28,276.9 in 1943 to 11,548.5 in 1946 Despite the decrease in employees and exposure hours, the case frequencies showed significant increases The maximal percentage case frequency was 4.04 per cent of the total employees or a maximal value of 238.1 cases per million hours of exposure in 1946 The yearly averages of the frequencies in terms of exposure hours range from 63.5 to 238.1 accidents per million man-hours compared with the standard accepted level of 4.0 Such values characterize a definitely hazardous plant

Table XLVIII shows the percentage case frequencies of the chief manifestations of the occupational disease at Plant B For the entire period, the average number of cases per month (1.42) and the total number of cases (68) were the same for both the dermatologic and the respiratory tract disorders The percentage frequency values show a significant increase in the dermatologic cases during the reported period, with values of 0.72 per cent and 0.56 per cent obtained in 1943 and 1944, and 2.82

per cent obtained in 1946 For the respiratory tract manifestations, only a slight decrease is evident The highest value of 1 77 per cent was obtained in 1943 corresponding to values of 1 26 per cent and 1 22 per cent in 1945 and 1946. A significantly lower value of 0 63 per cent was obtained in 1944.

Table XLIX shows the case frequencies considered to arise from exposure to the beryllium substances The results illustrate the points made with respect to these substances under the general discussion of table XLVI For the entire period the average monthly percentage frequency indicates the following relative classification of the operations from the most hazardous to the least hazardous, beryllium fluoride, 1 46 per cent, beryllium sulfate, 1 04 per cent, beryllium metal, 0.37 per cent, and the beryllium copper alloy, 0 18 per cent.

Further analysis of respiratory and dermatologic manifestations indicates a difference between those caused by sulfate and by fluoride For the dermatologic manifestations, the average frequency obtained with the fluoride is higher than that obtained with the sulfate This is similar to the total fluoride and sulfate frequencies, with values of 0 98 per cent and 0 49 per cent respectively In the case of the respiratory manifestations, however, the sulfate frequency was 0 55 per cent, or slightly larger than the fluoride frequency of 0 48 per cent.

Survey of the Plant Conditions

A survey of the environment of Plant B was made by members of the Industrial Hygiene Section, Rochester Atomic Energy Project, in December 1946 * In addition to the primary purpose of providing information for toxicologic work at Rochester, this survey had several objectives These included (1) the characterization of known hazardous areas of the beryllium plant in terms of atmospheric dust and fume concentrations and particle size, (2) the procurement of various samples of industrial materials for subsequent development of methods for recovery and analysis, and (3) the testing of various types of atmospheric sampling devices for field use and the determination of their relative value when applied to beryllium industrial hygiene problems

At the plant a preliminary study was first made of the nature of each

* Additional personnel aiding in the collection of samples were Dr F Bryan and Mr R Wilson, Engineering Department, Atomic Energy Project, University of Rochester, Rochester, New York

of the various operations The most hazardous dust and fume areas in operation at the time were selected for sampling These included the beryllium metal and the beryllium fluoride furnaces. The ore treatment area was also selected, despite the lack of a history of toxic beryllium exposure in this area, because our inspection showed an extremely dusty area and suggested a future potential hazard at this site.

The Dust and Fume Survey Samples of the atmospheres present in and near the selected areas were taken by means of each of the following methods: the modified cascade impactor, the filter paper dust sampler, and the M.S.A. midget impinger.[472] The samples collected with the modified cascade impactor and the filter paper dust sampler were taken at a sampling rate of 14 L. per minute. Those collected with the midget impinger were taken at a sampling rate of 0.1 cubic foot per minute. Most of the collected samples were analyzed chemically for beryllium using the spectrographic method of analysis.[77-b] Recoveries of beryllium from the samples were made by methods developed by Dr W. Neuman and Mr M Cucci * Several of the samples collected in each area were analyzed for fluorine content by Dr F. Smith* using a modification of the Willard and Winter distillation and thorium alizarin titration

The results obtained for each of the areas surveyed are given in tables L, LI, and LII in terms of concentrations of beryllium or fluorine per cubic meter of air. Table LIII shows the particle-size mass distributions obtained with the modified cascade impactor at each of the areas

Beryllium Metal Furnace As shown in table L three operational phases of the beryllium metal furnace were sampled These included the pouring period, the coke-removal period, and the immediate period after operations. All of the samples taken during the pouring and coke-removal periods except samples No. 5, 6, and 14 were taken from positions of from 3 to 6 feet in front of the furnace opening. These sampling positions corresponded to the ones in which the men engaged in the operation were working During the pouring operations, the filter paper and the cascade impactor samples showed a range of beryllium concentrations varying from 1.43 to 4 71 mg./m.^{3} The impinger sample corresponding to these samples yielded a significantly lower beryllium concentration value of 0 293 mg./m.^{3} The beryllium air concentrations

* Atomic Energy Project, University of Rochester, Rochester, New York

TABLE L. ATMOSPHERIC DUST CONCENTRATION AT BERYLLIUM METAL FURNACE OF PLANT B

Sample no	Phase of operation	Sampling position	Time (P.M.)	Sampling method*	Sampling time (min)	Sample analysis (total in micrograms) Be	F	Atmospheric conc (mg/m³) Be	F
1	Pouring	3-6 ft in front of furnace opening	9:00-9:15	Ip	6	5.0	—	0.293	—
2	"	"	"	Fp	5	100.0	—	1.43	—
3	"	"	"	Fp	5	330	—	4.71	—
4	"	"	"	CI	15	328	—	1.56	—
5	"	Over top of the furnace	"	Ip	10	50.0	—	1.76	—
6	"	"	"	Ip	4	—	18.7	—	1.65
7	Coke removal	3-6 ft in front of furnace opening	9:15-9:30	Ip	4	0.8	—	0.070	—
8	"	"	"	Ip	4	0.7	—	0.062	—
9	"	"	"	Ip	6	1.0	—	0.059	—
10	"	"	"	Ip	3	0.7	—	0.082	—
11	"	"	"	Ip	4	—	12.9	—	0.757
12	"	"	"	Fp	10	1.5	—	0.110	—
13	"	"	"	CI	15	112	—	0.533	—
14		10 ft from door of furnace in outer room	"	Fp	10	—	54.3	—	0.387
15	After operations	"	9:30-10	Fp	15	—	12.8	—	0.061
16	"	"	"	CI	30	2.5	—	0.006	—

* Ip Midget impinger
Fp Filter paper dust sampler
CI Cascade impactor

Table LI. Atmospheric dust concentration at beryllium fluoride furnace of plant B

Sample no	Phase of operation	Sampling position	Time (P M)	Sampling method*	Sampling time (min)	Sample analysis (total in micrograms)		Atmospheric conc. (mg/m^3)	
						Be	F	Be	F
1	Pouring	3 ft from furnace opening	10 45–11·00	Ip	3	0 6	—	0 070	—
2	..	.. ..	..	Ip	3	0 5	—	0 059	—
3	..	.. ..	..	Ip	3	0 7	—	0 082	—
4	..	.. ..	..	Ip	3	—	499	—	58 2
5	..	6–8 ft from furnace opening	..	Fp	5	0 6	—	0 009	—
6	..	.. ..	..	Fp	10	0 3	—	0 002	—
7	..	.. ..	..	Fp	5	—	160 3	—	2.29
8	..	.. ..	..	CI	15	5 9	—	0 028	—
9	..	Outer alley 15 ft from doorway to furnace room	..	Ip	6	0 4	—	0 023	—
10	..	.. ..	..	Ip	5	0 2	—	0 014	—
11	..	20 ft. over top of furnace	..	Ip	6	—	1092	—	64.1
12	..	10 ft. from furnace mouth	11 00–11 30	CI	30	4 7	—	0 011	—
13	Immediately after pouring	In outer alley	..	CI	20	—	89 6	—	0.32

* Ip Midget impinger
Fp Filter paper dust sampler
CI Cascade impactor

TABLE LII ATMOSPHERIC DUST CONCENTRATION AT BERYLLIUM ORE TREATMENT OF PLANT B

Sample no	Phase of operation	Sampling position	Time (A.M.)	Sampling method*	Sampling time (min)	Sample analysis (total in micrograms)		Atmospheric conc (mg/m³)	
						Be	F	Be	F
1	Rotary kiln during operation	1½ ft. in front of discharge end of kiln	10–11	Ip	4	1.0	—	0.088	—
2	"	" "	"	Ip	15	—	1.3	—	0.031
3	"	" "	"	Fp	5	10.0	—	0.143	—
4	"	8 ft. to side of discharge end of kiln	"	Ip	4	1.4	—	0.123	—
5	"	" "	"	Fp	6	15.0	—	0.179	—
6	"	" "	"	CI	15	64.6	—	0.307	—
7	"	8 ft. at 45° angle from neck of kiln	"	CI	15	43.5	—	0.207	—
8	"	12 ft. to side of discharge end of kiln	"	CI	15	10.5	—	0.050	—
9	"	20 ft. to side of discharge end of kiln	"	Ip	15	—	[illegible].0	—	1.17
10	"	"	"	Fp	15	—	74.8	—	0.763
11	"	Elevated ramp to far side of room	"	Ip	4	2.0	—	0.176	—
12	"	" "	"	Ip	4	6.0	—	0.528	—

* Ip Midget impinger
Fp Filter paper dust sampler
CI Cascade impactor

TABLE LIII PARTICLE-SIZE MASS DISTRIBUTION* AT PLANT B

Operation	Phase	Sample no	Sampling position	Size-mass distribution: Major component	Median size (microns)	Geom St'd deviation σ_g	Type of distrib	90% Size limit (microns)
Beryllium metal furnace	Pouring	4	3–6 ft in front of furnace opening	Be metal	0.88	—	Atypical	1.72
	Coke removal	13	" "	"	0.84	—	"	1.12
	After operation	16	10 ft from door of furnace in outer room	"	1.47	—	"	5.8
Beryllium fluoride furnace	Pouring	8	6–8 ft from furnace opening	BeF_2	2.60	2.27	Normal	—
	"	12	10 ft from furnace mouth	"	2.32	2.24	"	—
	Immediately after pouring	13	In outer alley	"	Below 0.1	—	Atypical	1.5
Ore treatment	Rotary kiln during operation	6	8 ft to side of discharge end of kiln	Beryl ore	7.79	2.44	Normal	—
	"	7	8 ft at 45° angle from neck of kiln	"	2.95	2.08	"	—
	"	8	12 ft, from discharge end of kiln	"	10.0	2.57	"	—

* Determined with the modified cascade impactor

decreased during the coke-removal period as indicated by values of 0 110 mg/m.³ obtained with the filter paper sampler and 0 533 mg/m³ obtained with the cascade impactor The impinger also showed this decrease and also significantly lower concentrations than the other methods, a range of values of from 0 059 to 0 082 mg/m.³ were found. Correspondingly, the impinger values analyzed for fluoride showed a comparatively high value of 0.757 mg/m³ Two impinger samples were taken during the pouring phase in a position over the top of the furnace Sample No 5 analyzed for beryllium yielded 1 76 mg/m³, sample No 6 analyzed for fluoride 1 65 mg/m³ A filter paper sample taken during the coke removal from a position 10 feet from the door of the furnace room showed a fluoride concentration in the same range as that obtained within the furnace room (0 387 mg/m.³) A similar sample taken in the immediate period after operations indicated a decrease in fluoride concentration to a value of 0 061 mg/m³

All of the particle-size mass distributions obtained within this area showed an atypical form of distribution indicating a mixture of dust and fume sizes The size-mass medians and 90-per-cent–size limits given in table LIII show similar values obtained for the two phases of the operation Median values of 0 88 microns and 0 84 microns were obtained at the pouring and coke-removal operations The corresponding 90-per-cent–size limits were 1.72 and 1 12 microns respectively For the period after the operation in the area of the room outside the furnace room, larger particle sizes were found A mass median of 1 47 microns and a 90-per-cent–size limit of 5 8 microns were obtained

Beryllium Fluoride Furnace As shown in table LI, two operational phases of the beryllium fluoride furnace were sampled These included the pouring period and the period immediately after operations Starting from positions approximately 3 feet in front of the furnace opening, samples were taken during the pouring period at varying distances extending into the outer alley of the furnace room to approximate the area occupied by the man engaged in this operation In the case of this area, the impinger samples gave higher values than those collected with the filter paper dust sampler Samples collected with the cascade impactor were in the approximate range of those collected with the impinger Beryllium concentrations ranging from 0 059 to 0 070 mg/m³ were obtained at a position 3 feet in front of the furnace opening These

decreased in areas away from this position to a value of 0.014 mg./m.³ in the outer alley 15 feet from the doorway to the furnace room. The two filter paper samples at positions 6 to 8 feet from the furnace opening showed very low values of from 0.002 and 0.009 mg./m.³

The fluoride concentration in this area was of the order of one thousand times that of beryllium. A value of 58.2 mg./m.³ was obtained for an impinger sample collected in the 3-foot position where beryllium concentrations ranged from 0.059 to 0.082 mg./m.³ Corresponding to the low filter paper beryllium samples at 6- to 8-foot position, the filter paper sample analyzed for fluoride also showed a relatively high fluoride value (2.29 mg./m.³). An impinger sample taken from a position 20 feet above the furnace yielded a fluoride value of 64.1 mg./m.³, which is of the same order as the value obtained in front of the furnace. Sample 13 taken in the area of the outer alley immediately after the pouring operation shows the lowest fluoride value obtained, 0.32 mg./m.³ This value, however, is still larger than any of the beryllium concentrations obtained.

Both of the particle-size mass distributions obtained during the pouring operation showed normal types of distributions when analyzed as beryllium. As shown in table LIII similar results were obtained in both cases, the mass medians were 2.60 and 2.32 microns. Corresponding geometric standard deviations were 2.27 and 2.24. The sample taken immediately after operations and analyzed in terms of fluoride show this material to be present largely in the form of extremely small sizes. An atypical distribution was obtained in which the mass median size indicated a value below 0.1 micron. The 90-per-cent-size limit for this sample was found to be 1.5 microns.

Beryllium Ore Treatment. The results obtained during the period of operation of the rotary kiln drier are given in table LII in terms of atmospheric concentrations of beryllium and fluoride. Samples were collected at varying positions in this area ranging from 1½ feet in front of the discharge end of the kiln to the elevated ramp on the far side of the area. Except for sample No. 8, all impinger samples collected in this area indicated lower values of beryllium concentrations than corresponding values obtained with the cascade impactor and the filter paper dust sampler. In terms of fluoride concentration, however, the impinger samples gave higher values than those obtained with the other methods. The beryllium dust concentration showed a variation of from 0.050 to 0.528 mg./m.³

over the entire area with the highest concentration indicated in the region of the elevated ramp The atmospheric concentrations of fluoride were of the same order of magnitude as the beryllium dust concentrations, ranging from 0 031 to 1 17 mg/m ³ The results showed the lowest value present in the immediate vicinity of the rotary kiln, the value increasing in the direction of the elevated ramp.

Normal distributions were obtained for particle-size samples taken in this area. As shown in table LIII the mass median sizes obtained were very large, ranging from 2 95 to 10 0 microns, the corresponding geometric standard deviations ranging from 2 08 to 2 57

Analysis of Beryllium Ores During the plant survey considerable interest was aroused in the group by the fact that one of the varieties of beryl ore used in the plant processes was suspected of containing uranium or other radioactive substance According to available records, at least three varieties of beryl ore had been used in the period from 1943 to 1946 Approximately 30 per cent of the total ore used during 1946 was of the suspected variety

Spot samples of each of the types of ores were secured for radioactivity and chemical analyses In order to determine the possible atmospheric contaminants resulting from use of these ores, a quantity of settled dust found in the ore processing area was also removed for analysis

A preliminary test for radioactivity was made by placing the ore specimens over a sheet of X-ray film protected by a 1/16-inch cardboard envelope After exposure for twenty-two hours a definite autoradiograph was produced with the suspected ore No traces of radiation were detectable in the other ore specimens

The ore specimens and the settled dust specimen were analyzed for beta activity by Mr. R Hayes * Table LIV shows the results obtained in terms of per cent of uranium by weight necessary to produce equivalent beta activity Results are also given for spectrochemical analyses of each sample.

In terms of beta activity only the suspected ore type (Beryl ore A) showed a significant amount of radioactivity All other samples showed values low enough to be within the background count or error of the analytical method

* Service Division, Department of Radiology, Atomic Energy Project, University of Rochester, Rochester, New York

decreased in areas away from this position to a value of 0 014 mg./m.³ in the outer alley 15 feet from the doorway to the furnace room. The two filter paper samples at positions 6 to 8 feet from the furnace opening showed very low values of from 0 002 and 0 009 mg./m.³

The fluoride concentration in this area was of the order of one thousand times that of beryllium. A value of 58.2 mg./m.³ was obtained for an impinger sample collected in the 3-foot position where beryllium concentrations ranged from 0.059 to 0 082 mg./m.³ Corresponding to the low filter paper beryllium samples at 6- to 8-foot position, the filter paper sample analyzed for fluoride also showed a relatively high fluoride value (2.29 mg./m.³). An impinger sample taken from a position 20 feet above the furnace yielded a fluoride value of 64 1 mg./m.³, which is of the same order as the value obtained in front of the furnace. Sample 13 taken in the area of the outer alley immediately after the pouring operation shows the lowest fluoride value obtained, 0.32 mg./m.³ This value, however, is still larger than any of the beryllium concentrations obtained.

Both of the particle-size mass distributions obtained during the pouring operation showed normal types of distributions when analyzed as beryllium. As shown in table LIII similar results were obtained in both cases, the mass medians were 2 60 and 2.32 microns. Corresponding geometric standard deviations were 2.27 and 2.24. The sample taken immediately after operations and analyzed in terms of fluoride show this material to be present largely in the form of extremely small sizes. An atypical distribution was obtained in which the mass median size indicated a value below 0.1 micron The 90-per-cent–size limit for this sample was found to be 1.5 microns.

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over the entire area with the highest concentration indicated in the region of the elevated ramp The atmospheric concentrations of fluoride were of the same order of magnitude as the beryllium dust concentrations, ranging from 0.031 to 1.17 mg./m.³ The results showed the lowest value present in the immediate vicinity of the rotary kiln, the value increasing in the direction of the elevated ramp.

Normal distributions were obtained for particle-size samples taken in this area As shown in table LIII the mass median sizes obtained were very large, ranging from 2.95 to 10.0 microns, the corresponding geometric standard deviations ranging from 2.08 to 2.57

Analysis of Beryllium Ores During the plant survey considerable interest was aroused in the group by the fact that one of the varieties of beryl ore used in the plant processes was suspected of containing uranium or other radioactive substance According to available records, at least three varieties of beryl ore had been used in the period from 1943 to 1946 Approximately 30 per cent of the total ore used during 1946 was of the suspected variety.

Spot samples of each of the types of ores were secured for radioactivity and chemical analyses In order to determine the possible atmospheric contaminants resulting from use of these ores, a quantity of settled dust found in the ore processing area was also removed for analysis.

A preliminary test for radioactivity was made by placing the ore specimens over a sheet of X-ray film protected by a 1/16-inch cardboard envelope. After exposure for twenty-two hours a definite autoradiograph was produced with the suspected ore No traces of radiation were detectable in the other ore specimens

The ore specimens and the settled dust specimen were analyzed for beta activity by Mr R. Hayes * Table LIV shows the results obtained in terms of per cent of uranium by weight necessary to produce equivalent beta activity Results are also given for spectrochemical analyses of each sample

In terms of beta activity only the suspected ore type (Beryl ore A) showed a significant amount of radioactivity All other samples showed values low enough to be within the background count or error of the analytical method

* Service Division, Department of Radiology, Atomic Energy Project, University of Rochester, Rochester, New York

The spectrographic analysis consisted of two types: a rough qualitative analysis and an accurate, quantitative analysis of the important constituents For the qualitative analysis all samples showed the presence of beryllium, aluminum, silicon, and small traces of iron. None of the samples showed any detectable amounts of arsenic, cadmium, mercury, or

TABLE LIV ANALYSIS OF BERYLLIUM ORE SAMPLES AT PLANT B

Sample	*Description of Sample*	*% uranium by weight necessary to produce equivalent beta activity*	*Spectrographic analysis*
Beryl ore A*	Irregular crushed rock fragments and crystals, light earth brown streaked with yellow "frost"	12 6	Qual.: Be, Al, Si, traces Fe Quant.: 5 0% Be, 4 0% U, 0 4% Th, 0 4% Pb
Beryl ore B	Irregular crushed rock fragments and crystals, pale translucent blue streaked with white quartz (pure beryl)	Less than 0 004	Qual Be, Al, Si, traces Fe Quant : 4 8% Be
Beryl ore C	Irregular crushed rock fragments and crystals, mixed light earth brown and pale green, infiltrated with quartz and mica	Less than 0 004	Qual Be, Al, Si, traces Fe Quant. 5 0% Be
Settled ore dust (Processing room)	Light earth brown showing many quartz-like crystals About 200 mesh size	Less than 0 006	Qual Be, Al, Si, traces Fe Quant 4 8% Be, 0 03% Pb

* Ore suspected of containing radioactive materials

thallium Although the beryl ore sample A and the settled ore dust both showed the presence of lead, only the ore sample A contained uranium and other radioactive materials

The quantitative spectrographic analysis of all samples showed the beryllium content to be approximately the same, 4 8–5 0 per cent The analysis of the beryl ore sample A showed the presence of 4 0 per cent uranium, and 0 4 per cent each of thorium and lead. The lead content of the settled ore dust was insignificant with a value of only 0 03 per cent.

Discussion

The most hazardous of the three areas surveyed were those of the beryllium metal furnace and the beryllium fluoride furnace Since these

operations represent short exposure [illegible] order of one-half hour or less, the results obtained in this [illegible] that very low levels of atmospheric concentration or [illegible] be toxic.

The relatively high fluoride concentrat[illegible] in the [illegible] areas are of particular significance since [illegible] present a hazard by themselves and also suggest a combined action with beryllium. Further study of this factor is required, especially in the case of the beryllium fluoride furnace where the relative fluoride concentration was 1000 times that of beryllium.

The results obtained show that for an industrial hygiene survey involving beryllium several types of sampling devices are required. For the insoluble beryllium dust, the filter paper dust sampler and the cascade impactor gave better concentration values than the midget impinger. In the case of fluorine concentration and the soluble beryllium fluorides, however, the results indicate better values were obtained with the midget impinger. Excellent particle-size results were obtained with the Cascade impactor, however, several preliminary samples taken on glass slides in the furnace areas indicated the presence of many fume sizes and aggregates of small particles. This indicates the necessity of further study of such areas using an instrument such as the thermal precipitator.

The presence of radioactive materials showing the high beta activity characteristic of beryl ore Type A indicates a considerable radon and thoron hazard. The absence of this activity in the processed ore dust suggests that the radioactive materials are removed during the first operations (crushing, and preliminary heat treatment) or that ore of the type considered was not being processed during the period of the December 1946, survey. An additional point of interest is that no specific history of poisoning has been reported in the pre-processing area. These results suggest the possibility of uranium and other radioactive materials acting synergistically or predisposing the cases of acute beryllium poisoning reported. Further study of this aspect of the problem is indicated.

Summary

A survey has been made of industrial health conditions of a beryllium plant in which many instances of beryllium poisoning have existed. The survey included an analysis of the dust and fume data taken under

operating conditions at the plant. The results of this analysis have been correlated with the medical history of the plant.

The plant in question produces a technically pure beryllium metal and beryllium-copper alloy. The operations involve grinding beryl ore, sintering, conversion to the sulfate with sulfuric acid, furnacing to the oxide, and treatment of the oxide by acid fluoride, followed by a reduction of the beryllium fluoride to yield metallic beryllium. The beryllium-copper alloy is made by heating copper with beryllium oxide in the presence of carbon. The atmospheric contamination associated with these processes is in the form of dusts, fumes, and mists. Selected areas were sampled, the selection being based on past medical history of hazard or on obvious contamination at the time of the survey. Sites selected were the ore-treatment area and that about the beryllium fluoride and beryllium metal furnaces. Sampling equipment consisted of a modified cascade impactor, filter paper dust sampler, and an M.S.A. midget impinger. Samples were analyzed in most instances for both beryllium and fluoride.

Of the three areas surveyed, those of the beryllium fluoride and beryllium metal furnace showed the most hazardous concentrations of beryllium and fluoride. Most arresting was the disproportionately high fluoride concentration near the fluoride furnace. Concentrations 1000-fold that of beryllium were found. Such high concentration of fluoride may represent a hazard in itself. The concentration of beryllium 3 feet from the furnace opening during the pouring operation was approximately 0.065 mg./m.³ During the pouring operation of the beryllium metal furnace, beryllium concentrations varied from 1.4 to 4.7 mg./m.³ at approximately 3 feet from the furnace. Samples for fluoride in this site were of the order of 1.7 mg./m.³. Near the rotary kiln drier for beryllium ore treatment, beryllium dust concentration varied from 0.050 to 0.53 mg./m.³; fluoride concentrations in the air were of the same order of magnitude. A particle-size analysis of the air contamination samples by means of the cascade impactor showed a mass-median particle size of 0.86 microns in the vicinity of the beryllium metal furnace, 2.46 microns next to the beryllium fluoride furnace, but sizes up to 10 microns in the area about the ore treatment room. The insoluble beryllium dusts were most efficiently sampled by either the cascade impactor or the filter paper dust sampler, but the midget impinger gave more satisfactory recoveries for soluble beryllium fumes.

Another problem investigated was that of beryl ores suspected of containing radioactive impurities One of three suspected ores showed significant beta activity equivalent to 12 6 per cent uranium, which on spectrochemical analysis later revealed 4 per cent uranium, 0 4 per cent thorium, and 0 4 per cent lead This degree of activity represents a definite thoron or radon hazard and suggests the possibility that uranium or other radioactive materials may act synergistically or as predisposing agents in beryllium poisoning

The medical history of the plant over a four-year period from 1943 to 1946 showed 136 cases of beryllium poisoning Cases for the most part were confined to the preparation of the sulfate, the fluoride, the metal, and the beryllium-copper alloy The symptoms of exposure were confined chiefly to the skin and respiratory tract The former was characterized by dermatitis and skin ulcer, and accounted for 50 per cent of all cases The dermatitis, affecting exposed areas of the skin, was often severe, being of the edematous, papulovesicular type When the face was involved, there was invariably associated conjunctivitis An element of sensitivity was believed to be demonstrated It was not uncommon to find individuals showing both dermatitis and bronchitis, especially if permitted to continue work in the areas of the sulfating process and fluoride furnace Chemical pneumonitis presented the severest type of beryllium poisoning and occurred among workers without respect to type of process. Several deaths from this cause were reported in 1943, typical symptoms were cough, substernal pain, shortness of breath, cyanosis, anorexia, weight loss, and increasing fatigue Vital capacity was reduced There was a low-grade fever Recovery did not occur if work was continued Examination of lung tissue sections showed a large number of plasma cells, diffuse pulmonary edema, and hemorrhage Roentgenograms of the lungs were diagnostic

Previous to 1943 the plant had experienced relatively little trouble, but increase in intensity of operations with the outbreak of the war, together with loss of trained and selected personnel by the operation of the draft, may be listed as possible factors responsible for an epidemic effect

The general plant history showed a shift in the number of cases through the years 1943-1946 During 1943 and 1944, the sulfate and beryllium-copper processes were particularly involved Following improved conditions at this site, the production emphasis shifted to beryllium fluoride

and beryllium metal where, at present, the greatest proportion of cases now appear (1946). The number of cases ranged from 63.5 to 238.1 per million man-hours of exposure, whereas the acceptable number in well-established chemical industries is 4.

CHAPTER 24

Summary of the Beryllium Problem in Connection with Atomic Energy Production

JOE W HOWLAND, M D *

To construct a research summary which represents the true worth of a series of related experiments is difficult even when conditions are ideal This would imply a sense of completeness of the individual problem, a definite interrelationship of the results, and a sense of immediate application Some type of answer can usually be found for questions which preface every toxicology problem, namely the type and extent of the toxicity, the mechanism by which toxicity is produced, and the possible therapeutic evaluations and control measures In all of these things, the summary of this work is unsatisfactory and in no small part discouraging. After considerable review and digestion of the facts presented today one is impressed with two pertinent findings

1 Analytical methods have been developed which are adequate for the needs of the general survey problem but are definitely unsatisfactory for use in the study of biologic materials
2 More importantly the combined efforts of the group have been unable to produce in six species of animals a laboratory equivalent of the clinical picture as seen in industrial workers with the acute type of beryllium intoxication, namely pneumonitis Up to the present time, at least, this also applies as well to the development of the granulomatous lesion of the chronic disease

It would undoubtedly be most beneficial to discuss these experiments in the light of the variations in findings between animals and humans In this way, a much better unity in general organization can be obtained

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Again it may be possible that light can be thrown on some of the discrepancies which exist and possible solutions suggested.

It is unnecessary to review the rather concise clinical and pathologic picture of acute beryllium poisoning which has been reviewed at length in other papers already presented. The findings in animals are considerably different and as might be expected vary with the species and relate to the routes of administration. Intratracheal injection and inhalation of toxic dusts and fume produce lesions in the lungs consisting of hemorrhage, edema, focal atelectasis, and inflammatory exudate. No diffuse interstitial infiltration was noted. Secondary foci appeared in the liver where central necrosis of cells was observed and in the kidney with necrosis of tubular epithelium Administration of beryllium salts by other routes produced similar changes, with less involvement of the skin and with irritative lesions of the eye, i e, conjunctivitis and keratitis

Laboratory findings likewise show no comparative significance. Where the blood changes in humans are largely limited to those secondary effects arising from ineffective respiration of the tissues (relative polycythemia and slight increase in abnormal cells related to an active marrow) the changes in animals show at maximum effect the development of a secondary anemia of normocytic type, a mild leukocytosis, and an increase in circulating platelets.

Blood and urinary analyses revealed no significant effect which is consistent in all species From this one would interpret the kidney and liver damage to be of relatively mild extent on a general basis Individual animal groups (rats and mice) did show evidence of kidney and liver injury Findings in human cases to date have been likewise normal, to all extent and purpose.

Recovery phenomena in the acute poisoning are of interest in that these alone appear to be roughly parallel The acute pathology of beryllium and its compounds in both man and animals leaves behind it no demonstrable effect on the involved organs, as far as is known

From the laboratory findings presented in this symposium it is possible to list many generalizations which may be of significant nature and of value. (1) That the toxicity varies in general with the solubility of the compound, the more soluble forms showing the greatest toxicity. By inhalation the soluble forms tend to produce an acute effect and early mortality and the insoluble ones, chronic effects and perhaps late mortality.

(2) That a definite species sensitivity exists. The guinea pig and hamster appear to be the most resistant species, the rabbit and mouse the most sensitive. (3) That amounts of soluble beryllium compounds in excess of 2 per cent of the diet cause a depression in weight of rats. Amounts up to 10 per cent of insoluble forms tested caused no reaction. Toxic manifestations included the beryllium rickets syndrome (4) That extraneous agents acting in combination with beryllium have not enhanced the effect or altered the type of pathologic response. Those agents studied include physical stress, bacteriologic agents, chemical poisons of known effect, and sensitization in reactive species (5) That analytical methods are being perfected including those of radioactive or tracer nature (6) That no granulomatous lesions have developed in animals surviving a period of six to eight months

The survey and clinical reports here presented require separate comment In the examination of the frequency of toxicity against the site of operation it was shown that the highest incidence in 136 cases of acute poisoning occurred in the preparation of the sulfate, the fluoride, the copper alloy, and the metal Approximately 50 per cent were of dermatitis and ulceration, bronchitis and pneumonitis constituting the remainder.

Surveys of the beryllium metal furnace and the fluoride furnace were carried out. During the pouring operation at the metal furnace the concentration of fume was 1 4 to 4 7 mg./m ^{3}, with a mass median particle size of 0 86 micron. At the fluoride furnace the concentration was 0 065 mg./m ^{3} with a particle size of 2 46 microns In other words, the insoluble form had the greatest concentration and the smallest particle size Toxic effects had been noted in the area, the soluble form had the least concentration and the greatest particle size (still within alveolar inhalation limits) and also produced symptoms Analyses of the fluoride in the latter area showed a concentration of fluoride 1000 times greater than beryllium, a significant factor not to be overlooked

Comment was raised as to the potential possibility of a synergistic action of radioactive materials contaminating the beryl ore These included uranium, thorium, and lead, in that order of importance

A definite indication does exist that preventive measures such as enclosure and ventilation of hazardous areas will act toward reduction of the incidence of cases of toxicity

PART FIVE

The Beryllium Problem

Experimental Aspects

CHAPTER 25

Animal Methods

ARTHUR J. VORWALD, M.D.*

Experimental studies concerning the pulmonary disease observed in beryllium workers constitute a major effort of the Saranac Laboratory at the present time Many were initiated originally by the late Dr Gardner and some of the observations reported here were recorded by him before his death Since that time additional observations have been made and a number of new experiments have been started In general, the research program to date has been designed to study the chronic type of lesion seen in the lungs of beryllium workers The acute inflammatory responses were of interest only insofar as they bore a possible relationship to the chronic lesion That lesion in the lung is diffuse and consists of large mononuclear cells, lymphocytes and plasma cells It is accompanied by giant cells with or without inclusion bodies Ultimately, focal necrosis, fibrosis, and hyalinization may be prominent

The biologic activity of a specific dust in contact with living tissue may be ascertained experimentally by an injection method or by an inhalation method In the former the dust, either dry or suspended in fluid, is injected into the test animal by one or several technics, including the subcutaneous, intraperitoneal, intracardial, intravenous, and intratracheal Such technics offer certain advantages contact between the tissue and the dust particles is assured, the protective mechanisms which may prevent the inhalation of dust never come into play, and the amount and state of dispersion of the injected material can be controlled rather accurately so that responses to different kinds of dust can be compared with a high degree of precision Another advantage is that injection experiments yield information about toxic properties of the dust rather early

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It is upon long-term inhalation experiments, however, that chief reliance is placed. Whether or not a dust, even though potentially hazardous, can be inhaled from atmospheric suspension, pass the natural defense barriers of the upper respiratory tract and gain access to the pulmonary parenchyma in quantities sufficient to produce damage can be determined only by inhalation procedures They are accomplished by placing groups of animals in an 8-foot cubical dust room containing a cloud of atmospheric dust mechanically generated by a special apparatus. The controlled dust cloud is maintained in the air for eight hours a day, five and a half days a week, for the balance of the time the dust is allowed to settle, but a small amount remains suspended indefinitely. Natural circulation of the air provides adequate ventilation in the room The animals are exposed in the dust rooms for long periods, up to three years or even longer, and at intervals during the experiment a few animals are sacrificed and the tissue examined to determine the nature and extent of the reaction Also, in some cases, animals are X-rayed periodically so that the course of the disease can be followed more closely.

The experimental investigations involve a number of substances containing beryllium which were introduced, either alone or in combination with other materials, into animals of various species by a number of methods For simplicity, the results of some of the investigations have been condensed and the essential data given in tabular form In the various tables are listed the substances studied, together with other pertinent information, including the animal species used, method employed, dosage of material, period of observation and, finally, the character of the inflammatory tissue reaction For identifying the nature of the reaction the following symbols have been employed.

- A Acute reaction animal dies within a few days, or even a few hours, after injection
- ± Minimum reaction mere ingestion of the substance by large mononuclear cells but without apparent damage to the cells.
- \+ Slight irritation: mild lymphocytic and large mononuclear cell reaction indicative of slight irritation about dust particles
- 2+ Moderate irritation· focal lymphocytic and large mononuclear cell reaction immediately about visible deposits of the substance.

3+ Advanced irritation: focal lymphocytic and large mononuclear cell reaction with proliferation of local tissue cells and mild fibrosis indicative of irritation but failing to reproduce the typical lesion seen in human cases.

4+ Reproduction of the typical lesion seen in humans focal and diffuse cellular reaction with the development of the granulomatous lesion consisting of a loose aggregate of large mononuclear cells surrounded by a peripheral zone of lymphocytes and plasma cells, and with (or without) giant cells, conchoidal bodies, necrosis, fibrosis, and hyalinization.

T Tumor osteochondrosarcoma

0 No reaction

In reviewing this classification, it will be noted that 4+ has reference to the typical lesion observed in human cases of the disease and 3+ is a severe reaction which, though not the same as that seen in humans, may be very close to it The symbol 2+ indicates mild irritation, + represents slight irritation, and ±, no definite toxicity.

For logical presentation of our findings it seems appropriate to consider first the soluble compounds Beryllium nitrate (table LV), injected intravenously in rabbits, proved to be very toxic, the animals dying within three days after the first injection In an attempt to influence the toxic reaction to the nitrate, the chemical agent BAL (2,3-dimercaptopropanol, known as British anti-lewisite), which has been employed to counteract metal poisoning, was mixed with beryllium nitrate and with beryllium metal powder and given to rabbits There was no protection, as the animals died in two to five days with an acute reaction Beryllium sulfate crystals implanted intraperitoneally in guinea pigs caused the death of the animals within two days, the same material implanted subcutaneously produced necrosis of cells and a response comparable to that seen around a foreign body—a ± reaction Beryllium sulfate was also employed in an inhalation experiment (table LVI) as a mist which guinea pigs inhaled for three hours a day for periods lasting from two and a half to four and a quarter months No deaths or pulmonary lesions were caused by the exposure. There were some widely-scattered large mononuclear phagocytes lying free in the pulmonary alveoli. The liver of these animals showed an occasional small focal area of necrosis, with a peripheral zone of lymphocytes The reaction was rated as 2+ and resulted apparently from hepatic localization of the inhaled substance.

TABLE LV SUMMARY OF INJECTION EXPERIMENTS WITH BERYLLIUM METAL AND BERYLLIUM COMPOUNDS

Substance	*Animal species*	*Injection method*	*Dosage*	*Period of observation*	*Tissue reaction*
SOLUBLE COMPOUNDS OF BERYLLIUM					
Beryllium nitrate	Rabbit	Intravenous	20 5 mg	3 days	A
Beryllium nitrate (plus BAL)	Rabbit	Intravenous	20 5	5	A
Beryllium sulfate	G Pig	Intraperitoneal	Few crystals	2	A
Beryllium sulfate	G Pig	Subcutaneous	Few crystals	45	±
INSOLUBLE COMPOUNDS OF BERYLLIUM					
Beryllium metal	G Pig	Intratracheal	75 mg	3 months	A-2+
Beryllium metal	G Pig	Intraperitoneal	200	5	+
Beryllium metal	Rabbit	Intravenous	1 gm.	8	2+
Beryllium metal (plus BAL)	Rabbit	Intravenous	20 5 mg.	5 days	A
Beryllium hydroxide	Rabbit	Intravenous	100	2 months	A-3+
Beryllium hydroxide	G Pig	Intraperitoneal	200	7	2+
Beryllium hydroxide	G. Pig	Intratracheal	150	4	3+
Beryllium oxide	G Pig	Intraperitoneal	200	7	2+
Beryllium oxide	G Pig	Intratracheal	150	9	2+
Beryllium oxide	Rabbit	Intravenous	1 gm	12	3+-T
Beryllium oxide	Rat	Intravenous	65 mg.	8	2-3+
Beryllium carbide	G Pig	Intraperitoneal	200 mg.	5 months	2+
Beryllium phosphate	Rat	Intravenous	5	21 days	A
Beryllium phosphate	Mouse	Intravenous	1	21	A
Beryllium phosphate	G Pig	Intracardial	15-25	21	A
Beryllium phosphate	Rabbit	Intravenous	103	10 months	T
Beryllium carbonate (basic)	Rabbit	Intravenous	50	4 days	A
Beryllium stearate	Rabbit	Intravenous	50	4	A
Beryllium stearate	Rabbit	Intravenous	100	25 months	2+
Beryllium stearate	G Pig	Intratracheal	150	12	3+

The insoluble forms of beryllium and its compounds (table LV) produced reactions of different degree and character which varied according to the form of the dust and the experimental method employed Beryllium metal introduced intraperitoneally resulted in the formation of black dust plaques on the peritoneal surface At four months and nineteen days, they were visualized in the gross as scattered, encapsulated masses that projected above the surface (fig 137). The masses consisted of a central area of dust and necrotic cells surrounded by a thick zone of dust-filled phagocytes, lymphocytes and few leukocytes enclosed by a

TABLE LVI SUMMARY OF INHALATION EXPERIMENTS WITH SUBSTANCES CONTAINING BERYLLIUM

Substance	*Animal species*	*Daily exposure*	*Maximum duration of exposure*	*Tissue reaction*
SOLUBLE				
Beryllium sulfate (mist)	G Pig	3 hours	4 months	Lungs–0 Liver–2+
INSOLUBLE				
Zinc beryllium manganese silicate	G Pig	8 hours	40* months	+
	Rabbit†	8	40*	3+

* For the first 15 months a material containing 2 30% BeO was used, for the remaining 25 months material having a BeO content of 13 06% was used

† Some of the rabbits inhaled dust that had passed under an ultraviolet lamp



FIG 137 Encapsulated mass of beryllium metal powder on the peritoneal surface 4 months and 19 days after injection into the abdominal cavity of a guinea pig × 10.

fibrous tissue capsule (fig 138) The reaction was classified as 1+, the type usually produced by the intraperitoneal injection of any dust. Intravenous injection of as much as one gram of beryllium metal caused only moderate reaction Observations eight months after the last injection revealed mild focal accumulations of large mononuclear cells, lymphocytes, and leukocytes about deposits of dust in the perilobular zones Fibrosis was not evident The tissue response was identified as 2+ reaction (fig 139) The chemical agent BAL failed to neutralize the action



Fig. 138 Higher magnification of fig 137 showing the black deposit of beryllium metal dust surrounded by a zone of necrotic debris, inflammatory cells, and a thin capsule of fibrous tissue



Fig 139 Reaction in the liver of a rabbit 8 months after intravenous injection of 1 gm of beryllium metal powder. It consists of a loose infiltration of lymphocytes and plasma cells

In fact, the combination stimulated an acute response and caused death of the rabbits within five days The metal dust was also introduced intratracheally and intraperitoneally but the tissue reactions proved to be no more positive than already described

Beryllium hydroxide was injected intraperitoneally, intravenously, and

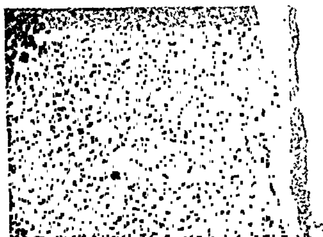


FIG 140 Peritoneal lesion of dust-filled macrophages, lymphocytes, and scattered giant cells in a guinea pig 7 months after injection of 200 mg of beryllium oxide into the abdominal cavity

intratracheally and the animals were observed up to seven months The reaction to intraperitoneal injection was 2+, that is, a moderate irritation consisting primarily of an area of dust and necrotic phagocytes surrounded by a thick fibrous tissue capsule often infiltrated with lymphocytes. Intravenous injection of 100 mg of the hydroxide caused death of one animal in three days from a generalized necrotizing reaction in the pulmonary tissue Another rabbit of this group survived for two months At that time it exhibited a delayed type of hepatic reaction classified as 3+ It should be noted that a 3+ lesion has large mononuclear cells with histiocytic proliferation and some fibrosis but not reproducing in any sense the granulomatous lesions of human cases of the disease Intratracheal injection also produced this type of reaction in the lung.

Beryllium oxide given intraperitoneally and intratracheally and observed for seven and nine months respectively caused a 2+ reaction

in the peritoneal cavity and in the lungs (figs. 140 and 141). Intravenous injection of this material into rabbits led to the formation of malignant tumors This important reaction will be referred to later.

Beryllium carbide was introduced intraperitoneally and the guinea



FIG. 141 Pulmonary lesion in a guinea pig about focal deposits of dust, 9 months after intratracheal injection of 150 mg. of beryllium oxide. It consists of a compact collection of inflammatory cells, predominantly dust-filled phagocytes, which fill the alveolar spaces and obliterate the pulmonary architecture.

pigs were observed for periods up to four and three-fourths months The reaction was 2+ (fig 142) Small and large, firm, dark gray dust plaques were scattered over the peritoneal surface These consisted of a central necrotic area laden with dust and containing distorted reticulum which was often hyalinized in the old lesion. Each lesion was surrounded by a zone of large mononuclear phagocytes and lymphocytes, few giant cells, and a peripheral thin fibrous tissue capsule

Beryllium phosphate was injected intravenously into rats and mice and intracardially into guinea pigs. All died from an acute necrosis of the liver within twenty-four hours to three weeks after the injection. The phosphate was also given to rabbits The longest observation period was ten months, by which time a malignant neoplasm had developed

Basic beryllium carbonate, introduced intravenously into rabbits, caused

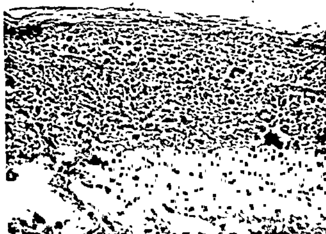


Fig 142 Cellular reaction about local deposits of beryllium carbide dust on the peritoneal surface of a guinea pig 145 days after intraperitoneal injection of 200 mg of the agent.

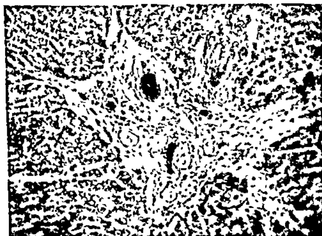


Fig 143 Moderate scarring and lymphocytic infiltration involving an occasional portal area in the liver of a rabbit 25 months after intravenous injection of beryllium stearate

profound hemorrhagic necrosis of the liver, massive hemorrhages into the spleen, and acute congestion of the lungs All animals died within four days following the single injection of 5 cc. of a 1% suspension of the agent

An organic salt, beryllium stearate, was used in an attempt to evaluate the action of beryllium combined with an organic acid radical. The salt



Fig 144 High magnification of a focal lesion in the lung of a guinea pig 12 months after intratracheal injection of 150 mg of beryllium stearate The alveolar walls are thickened and distorted with scattered lymphocytes, plasma cells, and large mononuclear phagocytes embedded in a network of connective tissue A single layer of epithelial cells lines many of the alveolar spaces, which contain scattered dust-laden macrophages in various stages of degeneration

was given intravenously to six rabbits in a single 50 mg dose. All animals died within a few days from an acute reaction The experiment was repeated with a total dose of 100 mg, but divided into twenty injections of 5 cc. of a 0.1% solution administered every three days The earliest reaction observed consisted of a mild round-cell infiltration in the portal areas of the liver. Much of this persisted, but the last animal, sacrificed twenty-five months after the last injection, exhibited also a thin network of fibrous tissue in some of the portal areas about the bile ducts. Necrosis or cirrhosis of the liver had not developed and the reaction was classified as 2+ (fig. 143) The lungs, spleen, kidneys, and bone marrow failed to exhibit significant change. Intratracheal injection of beryllium stearate

into guinea pigs caused a focal pulmonary reaction designated as 3+ (fig 144). The lesions consisted of slight proliferation of histiocytes accompanied by mononuclear cells, lymphocytes, and an occasional giant cell. In consequence, there was thickening of the alveolar walls with focal obliteration of the alveolar structure.

TABLE LVII SUMMARY OF INJECTION EXPERIMENTS WITH FLUORESCENT POWDER AND ITS COMPONENTS

Substance	*Animal species*	*Injection method*	*Dosage*	*Period of observation*	*Tissue reaction*
Zinc beryllium manganese silicate + Magnesium tungstate	G. Pig	Intratracheal	150 mg	12 months	3+
(Salvage tube powder)	G Pig	Intraperitoneal	200	6	2+
Zinc silicate (willemite)	G Pig	Intraperitoneal	200	13	±
Zinc silicate (willemite)	G Pig	Intratracheal	75	12	±
Zinc silicate (willemite)	Rabbit	Intravenous	1000	12	±
Manganese carbonate	G Pig	Intraperitoneal	200	4	±
Manganese carbonate	G Pig	Intratracheal	75	12	±
Magnesium tungstate	G Pig	Intraperitoneal	200	13	±
Magnesium tungstate	G Pig	Intratracheal	75	12	±
Magnesium tungstate	Rabbit	Intravenous	1000	12	±
Silicic acid prepared from ethyl silicate	G Pig	Intraperitoneal	200	1	±
	G Pig	Intratracheal	75	12	±
	Rabbit	Intravenous	1000	12	±
Silicic acid, preparation unknown	G Pig	Intraperitoneal	100-200	4	±
	G Pig	Intratracheal	50	12	±
	Rabbit	Intravenous	850	12	±

Attention is next directed to materials involved in the manufacture and use of fluorescent powders (table LVII) Since this product is of considerable industrial importance, many experiments were conducted with such powder and its components One of the first materials of this kind tested was a salvage tube powder recovered from broken fluorescent lamps. It consisted of a mixture of zinc beryllium manganese silicate and magnesium tungstate Intraperitoneal and intratracheal injection into guinea pigs (table LVII) produced a chronic type of reaction, followed for six months and one year, respectively. Intraperitoneally, the powder produced an encapsulated lesion with central necrosis of mononuclear cells, lymphocytes, and few giant cells Fibrosis did not take place When the dust was injected intratracheally, there occurred a progressive focal prolifera-

tion of tissue cells about scattered bronchioles and, finally, a localized stimulation of connective tissue in the lungs and bronchial nodes (fig 145). This reaction was identified as 3+. Subcutaneous implantations of the powder have not been observed long enough for analysis at this time. As a control, injection experiments were also conducted with zinc silicate,



FIG. 145 Low magnification of a focal reaction in the lung of a guinea pig 12 months after intratracheal injection of 150 mg of fluorescent tube powder The reaction is predominantly cellular but fails to reproduce the organization observed in lesions present in human cases.

manganese carbonate, magnesium tungstate, and two kinds of silicic acid (table LVII). In general, these compounds produced only a ± reaction consisting of a simple phagocytosis of the agents by large mononuclear cells, without any diffuse parenchymal involvement. One exception should be noted The silicic acid marked "preparation unknown" proved to be toxic and the standard doses killed the animals. However, if the material was injected in smaller doses over a longer period of time or if the animal survived the standard dose, complete resolution occurred with only a ± residual reaction evidenced by the presence of a few scattered focal accumulations of mononuclear cells and leukocytes.

A number of materials encountered in industrial processes associated with beryllium were employed in animal tests (table LVIII). Acid-treated slag was highly toxic. Injection of standard doses intratracheally and in-

TABLE LVIII SUMMARY OF INJECTION EXPERIMENTS WITH MISCELLANEOUS MATERIALS RELATED TO BERYLLIUM

Substance	*Animal species*	*Injection method*	*Dosage*	*Period of observation*	*Tissue reaction*
Slag (acid-treated dehydrated)	G Pig	Intraperitoneal	200 mg	10 days	A
	G Pig	Intraperitoneal	40	12 months	±
	G Pig	Intratracheal	20–50	20 days	A
	G Pig	Subcutaneous	50	2 months	±
Dross (mixture of copper and beryllium compounds)	G Pig	Intraperitoneal	2 cc –10%	1 day	A
	G Pig	Intraperitoneal	2 cc – 2%	2 days	A
	G Pig	Intraperitoneal	10 mg	12 months	±
	G Pig	Intratracheal	50	12	+
Frit (glass containing beryllium)	G Pig	Intraperitoneal	200	8	+
	G Pig	Intratracheal	150	8	2+

traperitoneally produced an acute inflammatory reaction with necrosis, hemorrhage, and edema. However, when given in smaller intraperitoneal doses or when localized subcutaneously, the dust became encapsulated, forming ± lesions. Dross, a complex mixture of copper and beryllium



FIG. 146 Low magnification of a focal lesion on the peritoneal surface of a guinea pig 8 months after injection of 200 mg. of frit into the abdominal cavity. The control area of dust and necrotic phagocytes is surrounded by a thick zone of cells and a thin capsule of fibrous tissue

compounds, on intraperitoneal injection of the standard dose was toxic and killed the test animals within one day. When the dose was reduced to 10 mg., the material was tolerated for twelve months, at which time only a ± reaction was observed consisting of scattered compact clumps of dust-filled mononuclear phagocytes and few giant cells. Necrosis, fibrosis, and encapsulation had not ensued. Injected intratracheally, dross produced no specific reaction after the initial acute response. At twelve



FIG. 147 Focal pulmonary lesion in a guinea pig 8 months after intratracheal injection of 150 mg of frit. The lesion is located about a terminal bronchiole and consists merely of lymphocytes, plasma cells, and large mononuclear cells containing dust particles

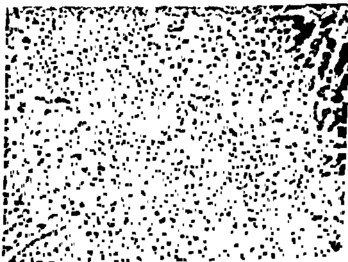


FIG 148 One of the widely distributed focal lesions in the liver of a dog, 2 weeks after intravenous injection of zinc beryllium manganese silicate powder Small areas of necrotic cells surrounded by lymphocytes, plasma cells, and large mononuclear cells constitute the reaction Proliferation of connective tissue is not evident Compare with fig 149

months, there was a small localized area of mild fibrosis with slight adenomatoid reaction and a few dust cells inside air spaces containing black clumps of dust. The reaction was nonspecific in type, 1+. Frit, a glassy substance, after being introduced intraperitoneally, became localized in small masses of necrotic dust cells surrounded by a zone of mono-

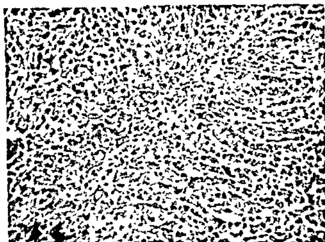


FIG 149 Mild lymphocytic infiltration, the only inflammatory response identified in the liver of a dog, 24 months after intravenous injection of zinc beryllium manganese silicate powder.

nuclear cells, few giant cells, and a thin connective tissue capsule (fig 146) Intratracheal injection of frit produced a focal inflammatory response limited to phagocytosis of the particles followed by slight fibrosis that became retrogressive Where the dust was highly concentrated, a moderately acute response leading to necrosis was observed Elsewhere the reaction consisted of large, dust-filled macrophages with an occasional giant cell in an alveolar space and only a slight histiocytic proliferation causing thickening of the alveolar wall (fig 147). The tracheobronchial nodes revealed diffuse infiltration with large, dust-filled mononuclear cells, but without fibrosis

Included also in the above group of materials were phosphorus "getters," substances composed of phosphorus alone or phosphorus plus a fluoride Three of these getters were tested (table LIX) An inhalation experiment was conducted with two of them It involved exposure of

guinea pigs for two hours daily over a period of twenty-one days, after which the pigs were removed to normal air and observed for as long as one year None of the animals exhibited evidence of toxicity and no tissue reaction was observed The third getter, red phosphorus, on injection intratracheally into a series of guinea pigs, caused an unusual reaction at sites of maximum localization, which included a pronounced accumulation of mononuclear cells with the formation of dense fibrous tissue Else-

TABLE LIX SUMMARY OF INHALATION AND INJECTION EXPERIMENTS WITH PHOSPHORUS "GETTERS"

Substance	*Animal species*	*Experimental method and dosage*	*Tissue reaction*
Mixture of 11% red phosphorus and 89% cryolite (sodium aluminum fluoride)	G Pig	Inhalation for 2 hours daily over a 21-day period, then observation for 1 year in normal air.	0
Mixture of 4% red phosphorus and 96% sodium iron fluoride	G. Pig	Inhalation for 2 hours daily over a 21-day period, then observation for 1 year in normal air.	0
Red phosphorus	G. Pig	Intratracheal injection of 7 5 mg of dust, reaction studied at 7 months	2+
Red phosphorus	G Pig	Intraperitoneal injection of 10 mg. of dust; reaction studied at 8 months	+

where, however, there was a low-grade focal reaction consisting of a few inflammatory cells but without effect on the surrounding alveolar walls. The reaction is difficult to classify, but probably should be called 2+. Injected intraperitoneally the phosphorus produced a + reaction of focal encapsulated masses without extension into the adjacent tissue.

The fluorescent powder, zinc beryllium manganese silicate, has been employed in numerous animal experiments. The formula of this powder has been changed a number of times In consequence, powders with a beryllium oxide content ranging from 2 30 to 13 06 per cent have been studied at the Saranac Laboratory. The 2 30 per cent BeO powder has been used in many injection tests (table LX). Following intravenous injection of the material into 2 dogs, one died immediately after receiving the fourth scheduled dose of 16 cc. of a 2 per cent solution, two weeks



Fig 150 Hepatic lymph node of the dog of fig 149 The sinuses are merely dilated with a loose collection of large mononuclear cells, a more specific type of reaction was not observed



Fig 151 Gross section of the lung of a guinea pig 6 months after intratracheal injection of zinc beryllium manganese silicate powder with a BeO content of 2 30 *per cent* *Small*, barely visible focal lesions are scattered throughout the lung mainly about the terminal bronchioles The tracheobronchial nodes are enlarged

after the first injection. Sections of the liver revealed scattered focal deposits of dust accompanied by local necrosis and mild infiltration of lymphocytes, plasma cells, and large mononuclear cells (fig. 148) The second dog remained well and healthy. It was sacrificed to terminate the experiment two years after the initial injection. The organs in the gross

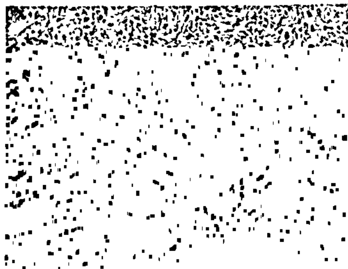


Fig 152 High magnification of a lesion in fig. 151 exhibiting the character of the proliferative reaction consisting of a compact collection of large mononuclear phagocytes in a thin network of connective tissue.

failed to reveal significant abnormality. Microscopically, the liver showed only a mild lymphocytic infiltration about deposits of dust (fig. 149). The hepatic node was hyperplastic with distention of the sinuses by large mononuclear cells, many of which contained visible particles of dust (fig. 150). The spleen and bone marrow were also hyperplastic. In general, the tissue reactions observed in the various organs failed to reproduce the lesions observed in human cases of the disease.

The 2 30 per cent BeO powder was introduced also into other species of animals. When injected intravenously into rabbits, there resulted the characteristic bone tumor to which reference will be made later On intraperitoneal injection, the dust became encapsulated on the peritoneal surfaces and the reaction was 2+. For guinea pigs also the reaction was 2+. Irradiation of the dust with ultraviolet light before injection failed to alter the response. On intracardial injection, the dust produced focal

lesions of lymphocytes and large mononuclear cells in the liver about the central vein The spleen, bone marrow, and lungs failed to reveal any significant alteration In rats, the reaction following intravenous injection was similar to that produced in guinea pigs Intratracheal injection into guinea pigs caused only scattered stellate lesions barely visible in the



FIG 153 Gross section of the lung of a guinea pig after 40 months exposure by inhalation to an atmosphere containing zinc beryllium manganese silicate The lesions are scattered throughout the lung, being localized mainly about the terminal bronchioles and associated with mild focal emphysema The tracheobronchial lymph nodes are enlarged

gross lung and slightly enlarged tracheobronchial nodes (fig 151) The pulmonary lesions exhibited a focal proliferation of cells with a mild fibrocytic type of reaction concentrated about scattered bronchioles (fig 152) Other organs were not involved The lesions were not like those observed in human cases of the disease They were classified as 3+ Intratracheal injection into rats produced a nontoxic response, classified as + and consisting of active monocytes about deposits of dust

In addition to the injection tests, an investigation with fluorescent powder has been conducted by the inhalation technique (table LVI) For a period of fifteen months guinea pigs and rabbits were exposed to atmospheric suspensions of the powder with 2 30 per cent BeO content

after the first injection Sections of the liver revealed scattered focal deposits of dust accompanied by local necrosis and mild infiltration of lymphocytes, plasma cells, and large mononuclear cells (fig 148). The *second* dog remained well and healthy. It was sacrificed to terminate the experiment two years after the initial injection. The *organs in the gross*



Fig 152 High magnification of a lesion in fig. 151 exhibiting the character of the proliferative reaction consisting of a compact collection of large mononuclear phagocytes in a thin network of connective tissue.

failed to reveal significant abnormality. Microscopically, the liver showed only a mild lymphocytic infiltration about deposits of dust (fig. 149). The hepatic node was hyperplastic with distention of the sinuses by large mononuclear cells, many of which contained visible particles of dust (fig 150) The spleen and bone marrow were also hyperplastic In general, the tissue reactions observed in the various organs failed to reproduce the lesions observed in human cases of the disease.

The 2 30 per cent BeO powder was introduced also into other species of animals When injected intravenously into rabbits, there resulted the characteristic bone tumor to which reference will be made later. On intraperitoneal injection, the dust became encapsulated on the peritoneal surfaces and the reaction was 2+. For guinea pigs also the reaction was 2+. Irradiation of the dust with ultraviolet light before injection failed to alter the response. On intracardial injection, the dust produced focal

lesions of lymphocytes and large mononuclear cells in the liver about the central vein The spleen, bone marrow, and lungs failed to reveal any significant alteration In rats, the reaction following intravenous injection was similar to that produced in guinea pigs. Intratracheal injection into guinea pigs caused only scattered stellate lesions barely visible in the



FIG 153 Gross section of the lung of a guinea pig after 40 months exposure by inhalation to an atmosphere containing zinc beryllium manganese silicate The lesions are scattered throughout the lung being localized mainly about the terminal bronchioles and associated with mild focal emphysema The tracheobronchial lymph nodes are enlarged

gross lung and slightly enlarged tracheobronchial nodes (fig. 151) The pulmonary lesions exhibited a focal proliferation of cells with a mild fibrocytic type of reaction concentrated about scattered bronchioles (fig. 152) Other organs were not involved The lesions were not like those observed in human cases of the disease They were classified as 3+ Intratracheal injection into rats produced a nontoxic response, classified as + and consisting of active monocytes about deposits of dust

In addition to the injection tests, an investigation with fluorescent powder has been conducted by the inhalation technique (table LVI). For a period of fifteen months guinea pigs and rabbits were exposed to atmospheric suspensions of the powder with 2.30 per cent BeO content.



Fig. 154 High magnification of a lesion in the lung shown in fig. 153 The alveolar spaces contain loose aggregates of dust-filled phagocytes The alveolar walls are only slightly thickened

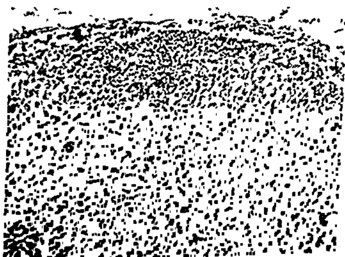


Fig. 155 High magnification of the enlarged tracheobronchial lymph node observed in fig. 153. It is apparent that the enlargement is due to infiltration of large mononuclear phagocytes and an occasional giant cell

Since no important reaction developed in the lungs of animals sacrificed for sampling, the pigs and rabbits were then exposed for an additional twenty-five months to a powder with 13 06 per cent BeO The atmospheric concentration of dust during these exposures ranged from 3 5 to 10 milligrams per cubic meter of air The gross lungs of guinea pigs living in that



Fig 156 Low magnification of a focal lesion in the lung of a rabbit after 40 months exposure by inhalation to an atmosphere containing zinc beryllium manganese silicate The exposure is comparable to that for the guinea pig shown in figs 153, 154, and 155 The lesion is irregular and occupies generally the alveolar walls, which are thickened The spaces contain a loose collection of cells and many are distorted and somewhat dilated

atmosphere for forty months revealed scattered small focal lesions localized mainly about the terminal bronchioles and, in addition, enlarged but soft tracheobronchial nodes (fig 153) Microscopically, the pulmonary lesions (fig 154) disclosed alveolar aggregates of dust-laden phagocytes accompanied by few lymphocytes, plasma cells, and an occasional giant cell The surrounding alveolar walls were only slightly thickened with cells The tracheobronchial nodes (fig 155) contained scattered dust cells confined for the most part to the sinusoidal areas but involving

also the germinal centers. The reaction failed to demonstrate any degree of specificity, being comparable to that resulting from the inhalation of dust producing only slight irritation. It was classified as +. Rabbits subjected to the same atmosphere exhibited also scattered small pulmonary lesions which by forty months were barely visible in the gross. Except



FIG 157 High magnification of the lesion in fig 156. Compare with fig. 154 The reaction in the thickened alveolar walls consists of scattered [illegible] stages of de- [illegible] phagocytes

for scattered dust cells in the alveolar spaces, the reaction involved mainly the alveolar walls (fig 156) It consisted of infiltrated lymphocytes, plasma cells, and proliferated histiocytes with the development of thin strands of connective tissue. Many of the spaces exhibited a thin membranous lining of epithelial cells (fig. 157), a common experimental finding in chronic inflammatory processes involving the lung. Thus, the pulmonary reaction to inhaled zinc beryllium silicate in the rabbit was more severe than in the guinea pig It was classified as 3+. However, it failed to demonstrate any specificity such as observed in clinical cases

Since it was suggested that ultraviolet light might, in some unknown manner, impart toxic properties to the fluorescent dust particles, a special group of animals (table LVI) were made to inhale the air-borne dust

after it had passed under an ultraviolet lamp The tissue reactions were no different from those resulting from the inhalation of the untreated dust

Some interesting findings were revealed by rabbits in which the fluorescent powder, 2 30 per cent BeO content, had been injected intratracheally (table LX) The first animal died one week after a single injection of 2 cc.

TABLE LX. SUMMARY OF INJECTION EXPERIMENTS WITH ZINC BERYLLIUM MANGANESE SILICATE POWDER

Beryllium content	*Animal species*	*Injection method*	*Dosage*	*Period of observation*	*Tissue reaction*
2 30% BeO	Dog	Intravenous	1 3 gm	24 months	Liver 2+ H L Node 2+
2 30% BeO	Rabbit	Intravenous	1	10	T
2 30% BeO	Rabbit	Intraperitoneal	40 mg	12	2+
2 30% BeO	Rabbit	Intratracheal	100 300	1 week to 12 months	3+
2 30% BeO	G Pig	Intracardial	80	22 months	2+
2 30% BeO	G Pig	Intraperitoneal	140-200	6 8	2+
2 30% BeO	G Pig	Intraperitoneal	*40	2	2+
2 30% BeO	G. Pig	Intraperitoneal	†40	4	2+
2 30% BeO	G Pig	Intratracheal	150	6	3+
2.30% BeO	Rat	Intravenous	80	12	2+
2 30% BeO	Rat	Intratracheal	20	12	+

* Dry irradiated powder used
† Dry non-irradiated powder used

of a 5 per cent suspension of the agent Grossly (fig 158), the lungs revealed confluent lesions concentrated bilaterally in the upper lobes but also scattered elsewhere as more isolated foci Microscopically, these early lesions exhibited a subacute type of reaction (Plate V, A) consisting of necrosis in areas of massive deposits of dust surrounded by large mononuclear cells and lymphocytes, which occluded the air spaces and infiltrated the alveolar walls Proliferation of local histiocytes was not a prominent feature The pulmonary architecture was generally obliterated, however, certain air spaces of varied sizes still persisted and many were lined by a single layer of epithelial cells Although such linings are a common feature in chronic inflammatory lesions of the lung, nevertheless, in this instance they appeared more conspicuous than usual The significance of the finding is not apparent unless it is an expression of unusual susceptibility of the particular rabbit to epithelial stimulation It was not present in animals sacrificed at one month, four months, eight



FIG 158 Cross section of the lung of a rabbit 1 week after intratracheal injection of 100 mg of zinc beryllium manganese silicate powder with a BeO content of 2 30 per cent. The reaction is localized mainly in the upper third with focal lesions scattered elsewhere The intervening pulmonary tissue is normal

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PLATE V.

A. High magnification of a pulmonary lesion in rabbit, fig 158, 1 week after intratracheal injection of 100 mg of zinc beryllium manganese silicate powder with a BeO content of 2 30 per cent It shows an irregular focus with massive quantities of dust, and cells in various stages of necrosis surrounded by infiltrated large mononuclear cells and lymphocytes Many of the capillaries are engorged with blood

B Detail of a lesion in the lung of rabbit, fig 159, 1 month after intratracheal injection of 300 mg of zinc beryllium manganese silicate powder with a BeO content of 2 30 per cent. Only a small focus of necrosis persists within an area of chronic inflammation in which strands of connective tissue are evident

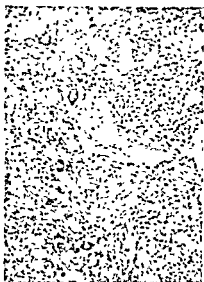
C High magnification of the reaction in the lung of a rabbit 8 months after intratracheal injection of 300 mg of zinc beryllium manganese silicate powder with a BeO content of 2.30 per cent, similar to rabbit, fig 158 Except for small areas of necrosis about local concentrations of dust, the reaction consists of compact masses of large dust-filled phagocytes and few scattered giant cells enmeshed in strands of connective tissue

D. High magnification of a pulmonary lesion in rabbit (fig 160) 12 months after intratracheal injection of 300 mg of zinc beryllium manganese silicate powder with a BeO content of 2 30 per cent. The lesion exhibits bands of connective tissue and scattered lymphocytes, plasma cells, and large mononuclear phagocytes Degeneration of cells is evident in local concentrations of dust.

A



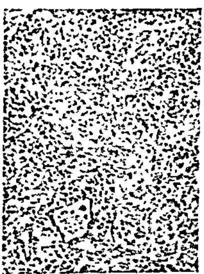
B



C



D



Caption on facing page



Fig 159 Cross section of the lung of a rabbit, injected like the rabbit of fig 158, 1 month after injection The reaction is concentrated in the upper third and in the hilar regions However it is more diffuse than at 1 week after injection



Fig 160 Cross section of the lung of a rabbit, injected like the rabbit of fig 158, 12 months after injection The lesions are irregular and localized about the bronchi, bronchioles, and vascular trunks in the hilar portions The tracheobronchial lymph nodes are only moderately enlarged

months, and twelve months after receiving a total dose of 300 mg in aliquots of 100 mg. given one week apart.

The rabbits sacrificed one, four, and eight months after injection again showed the reaction concentrated in the upper third of the lung (fig. 159) Microscopically (Plate V, B), these late reactions exhibited decreasing



FIG 161 Long bones in the upper extremities of a rabbit 8 months after intravenous injectic ... silicate (Be content 2 3 per cent ... The tumorous rarefaction of ... ident

amounts of necrosis, increasing proliferation of large mononuclear phagocytes and histiocytes with the formation of collagen and fibrous connective tissue By eight months (Plate V, C), the tissue reaction was characterized also by compact masses of large mononuclear cells and the presence of scattered giant cells.

By twelve months, the pulmonary reaction was less intense (fig 160) The lesions were localized mainly in the hilar portion of the lungs about the bronchi, bronchioles, and vascular trunks They were irregular and consisted of loose fibrous connective tissue, scattered lymphocytes and plasma cells (Plate V, D) Only an occasional small area of necrosis was present The large mononuclear cell response, so prominent in the eight months animal, was not a conspicuous feature at this late date

Thus, the results of the series of inhalation experiments and also of the

intratracheal injections suggest that the fluorescent powder is biologically active when introduced into the lungs of experimental rabbits and gives rise ultimately to pulmonary lesions classified as 3+.

In addition to the experiments outlined, others have been completed and many are still being carried on A great variety of conditions such as



Fig 162 Gross osteochondrosarcoma in the bones seen roentgenographically in fig 161

diet, dust inhalation during pregnancy, and the effect of infection have been studied in an attempt to reproduce the type of tissue reaction present in human cases In no instance, however, have we succeeded

Other experiments involved the production of malignant bone tumors in rabbits To date, at least five separate compounds of beryllium from various industrial sources have proved positive They may be identified as beryllium oxide, beryllium phosphate, and as zinc beryllium manganese silicate having values for BeO of 2 30, 8 27 and 13 06 per cent, respectively Beryllium metal and various beryllium compounds such as the hydroxide, carbonate, phosphate, nitrate, and silicate failed to produce such tumors. They have not developed in other species of animals such as guinea pigs and rats Furthermore, similar tumors have never been encountered during the injection of 75 different minerals into the ear veins of rabbits

The tumors usually become fully established from eight to ten months

monary lesions discovered in human cases There is no doubt that
clinical evidence collated is indeed highly suggestive However, it seem
pertinent that every effort be made to study the problem experimentall
if only to establish fully the etiology and pathogenesis of the disease and
to evolve, if possible, preventive and therapeutic measures.

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by means of compounds that were indicted in industry. I should like to
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into the study of the disease and as he works longer with these animal
he may eventually be willing to say that he has succeeded

Unfortunately, I have not had a chance to examine the slides made
from these animals, and while the reproductions which he showed are
highly suggestive, I can only base my comments on them.

We have been presented with a problem that is peculiar to beryllium
(more so, perhaps, than to some other industrial diseases) because of
apparent individual predisposition to the disease. By that I mean tha
two people will be working side by side, getting presumably the same
exposure One will burst out with a florid type of the disease, the other
will not be affected—at least, not immediately. Therein lies something
about which we must be on guard—the variability in the latent period.
Some of these people will develop pneumonitis at a considerable time
after their co-workers, similarly exposed, have already developed it. I
introduce this point because of its importance in animal experimentation,
which is the phase of the work that I am to discuss.

In dealing with animals, we must, of course, base our work on the

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fundamentals We must do enzyme studies and localization studies of beryllium in the tissues, and similar experiments But the one hard fact is that we want to produce the disease in animals to establish the pathogenicity of beryllium beyond all doubt, if it be pathogenic.

While these acute experiments are of some importance, therefore, the long, slow approach, the up-hill climb, is the one that is really going to get results that are of interest to industry

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It would seem to be a good policy to extend the experiments and introduce complicating factors which can be controlled I have reason to believe that experiments are being carried on in which other irritants are being utilized in conjunction with beryllium or its compounds, and it is quite possible, I think, that a disease quite like the human disease will be developed by the researchers who are engaged in that work

The other aspect of the problem, from the research angle, is the species difference which always is a problem in animal work To illustrate, Dr Vorwald has told us that Dr Gardner produced tumors with beryllium compounds in rabbits I feel quite certain that these tumors have not been produced in any other animals, and of course, the reason is still obscure.

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In our laboratory we have analyzed tissues from rabbits which we have exposed to beryllium by various methods and, I believe, have established levels compatible with what we would expect under the conditions of the experiments Furthermore, we have analyzed urine from people with chronic pneumonitis and have recovered small quantities of beryllium.

It seems to me that, in groping for a test for beryllium exposure before there is beryllium disease, or for patent beryllium disease before there is *clinical* beryllium disease, the best approach would be the direct analysis of urine for beryllium, rather than some roundabout and nonspecific method involving liver function or other biochemical tests

Further Discussion

MR. MORSE: In any of the experiments which led you to believe you were coming close to reproducing the lesion, was there exposure to dust with a BeO content below 13.06 per cent?

DR VORWALD Yes. We carried on experiments at 2.3 per cent and found no evidence of change, therefore, we increased it to a 13 06 BeO content for sixteen months

MR MORSE: There has been some exposure to the higher percentage?

DR. VORWALD. Yes, groups of guinea pigs and rabbits were exposed for prolonged periods to atmospheric concentrations of dust containing 13 06 per cent beryllium oxide.

DR MACHLE I have just a few questions of which one is essentially the one Mr Morse asked. You graded that of the rabbit receiving 2 3 per cent beryllium phosphor as a 3+?

DR. VORWALD Yes, each of the rabbits in the series referred to received an intratracheal injection once a week for three weeks. Each dose consisted of 2 cc of a 5% suspension of zinc beryllium manganese silicate containing 2 3 per cent beryllium oxide. We hesitated grading the pulmonary pathology as a 4+, feeling that the unit lesion seen in humans had not been reproduced, at least in eight months time. The experiments are continuing and it may be that later animals of the series will permit the higher grade

DR MACHLE: With reference to intraperitoneal injection of beryllium metal, do you remember the year in which the metal was procured?

DR VORWALD It was procured on or about June 1, 1946

DR MACHLE Was it previously purified?

DR VORWALD It was forwarded to us labelled "beryllium powder, 325 mesh" The X-ray diffraction pattern of this product revealed metallic beryllium and no other crystalline substances Therefore, we considered it to be of high purity

DR MACHLE It's an interesting point, because prior to 1946, beryllium metal had been about 96 to 99 per cent pure, the impurity being soluble beryllium salts, chloride or otherwise, incorporated as a slag in the metal itself, so we must take that into consideration in evaluating results applied to the metal alone

DR RICHARDSON Since I think we are more interested in the chronic or delayed type, I'd like to ask two questions Those cases I have seen in the human have had excessive fatigue due to overwork, either the result of long hours in the plant or to an outside activity Now, I wonder how much that could play a part in the animal experimentation if it were possible to introduce fatigue into the experiment

Secondly, I wish to call attention to the fact that these patients, in spite of a huge food intake, lose weight I would ask whether anything has been done to observe the metabolic rate in these cases.

DR. VORWALD Except for rather gross observations that the animals under experimentation have lost weight, we have not done metabolic studies It would be interesting to study the factor of fatigue However, circumstances of the experiment would make such studies rather complicated Dr Wright, do you wish to comment?

DR WRIGHT Those men we have studied here—and the studies were not exhaustive in any way—did seem to show a higher than zero or perfectly normal predicted basal metabolism They were not inordinately high, they ran around plus-twenty.

CHAPTER 26

Chemical Methods

THOMAS M. DURKAN*

Beryllium is a bivalent metal and behaves like aluminum in many chemical reactions Since it is an element not often encountered in ordinary industrial processes, analytical procedures for separating and determining beryllium in the presence of interfering substances have been studied less intensively than have technics for such common elements as iron and aluminum. Methods used for determining beryllium in materials like metallic alloys, minerals, and fluorescent powders are generally adequate, but in the case of biologic material procedures now available are not entirely satisfactory, because of incomplete recovery of the beryllium. However, Dr Neuman† has outlined two colorimetric methods and one fluorometric method, suitable for biologic samples, which will probably come into general use as soon as detailed procedures have been published. In the meantime research upon this problem is being carried on at the Trudeau Foundation laboratories and at other institutions. An extensive bibliography on analytical methods for beryllium appears in U. S Public Health Bulletin 181.[12]

The chemical methods for determining beryllium may be classified as gravimetric, colorimetric, and fluorometric. Gravimetric methods are best suited to samples containing several milligrams or more of beryllium, while for microgram quantities the colorimetric and fluorometric procedures are used These will be examined individually and the merits of each discussed.

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GRAVIMETRIC METHODS

When a substance is analyzed according to the usual scheme employed for minerals, beryllium is precipitated with ammonia after removal of silica and the hydrogen sulphide group In the case of alloys the heavy metals are removed by electrolysis with a mercury cathode before the ammonia precipitation Since the ammonia precipitate contains not only beryllium but probably other elements, such as iron and aluminum, a separation is necessary A number of technics for accomplishing this are listed as follows

1. Oxine (8-hydroxyquinoline)
2. Mercury cathode
3. Sodium hydroxide
4. Cupferron
5. Ether extraction
6. Ether-hydrochloric acid precipitation
7. Tannin
8. Sodium carbonate fusion

When the quantity of the interfering elements is small, the separation is best carried out with oxine (8-hydroxyquinoline), as described in Bureau of Standards Research Paper 813 [312] The excellent results obtained with this reagent are shown in table LXI Oxine forms insoluble com-

TABLE LXI DETERMINATION OF BERYLLIUM WITH OXINE

BeO taken (gm)	*First separation* (gm)	*Second separation* (gm.)	*BeO recovered* (gm)	*Error* (gm)
0 3004	0 2996	0 0006	0 3002	−0 0002
0 1502	0 1497	0 0005	0 1502	0 0000
0 0150	0 0150	0 0002	0 0152	+0 0002
0 0015	0 0014	0 0000	0 0014	−0 0001

OTHER ELEMENTS PRESENT (GM)
0 10 Al_2O_3 0 01 Fe_2O_3 0 005 TiO_2 0 005 ZrO_2

pounds with iron, aluminum, and titanium, while the beryllium, which remains in solution, can be precipitated in the filtrate with ammonia Although it is claimed that the precipitation of beryllium is complete even in the presence of the oxine reagent, this does not appear to be true

in all cases and it is safer to destroy the organic material with nitric and sulfuric acids before precipitating the beryllium. Two precautions should be observed: filtrates should stand overnight and be examined for any additional precipitate and the solution for washing the precipitate should be faintly alkaline.

There are several separations which are used occasionally either alone or preceding an oxine precipitation. As already mentioned, electrolysis with a mercury cathode can be employed to eliminate heavy metals such as iron, copper, and zinc, while aluminum and beryllium will remain in solution Other reagents useful for separating aluminum and beryllium from iron and various elements are a boiling solution of sodium hydroxide and the organic salt cupferron Extraction with ether is an easy way of removing large amounts of iron but a little is always left behind Beryllium can be separated from aluminum by the Gooch and Havens method,[19] in which the aluminum is precipitated as the chloride in a mixture of ether and hydrochloric acid, or by precipitation with tannin as described by Nichols and Schempf[411] Fusion with sodium carbonate followed by extraction with water is sometimes used to separate beryllium and phosphorus but tests indicate that more or less beryllium may go into solution with the phosphorus

Colorimetric Methods

Dr. Neuman described two colorimetric procedures which he studied and found satisfactory (table LXII) In one the color is produced with

Table LXII colorimetric methods

1,4-dihydroxyanthraquinone, 2-sulfonic acid
aurintricarboxylic acid (aluminon)
p-nitrobenzene-azo-orcinol

1, 4-dihydroxyanthraquinone, 2 sulfonic acid, and in the other with the reagent known as aluminon. A third method, developed in England by Osborne and Stross,[454] utilizes the dye p-nitrobenzene-azo-orcinol It was tested in the Saranac Laboratory but was regarded as unsuitable because of the deep color of the blank and lack of sensitivity.

Fluorometric Methods

The fluorometric technic would appear to be the method of choice for determining minute amounts of beryllium in biologic material, not only because of its great sensitivity but also because fewer substances interfere. Three reagents (table LXIII), have been used in fluorescent analysis for beryllium: morin, 1-amino-4-hydroxyanthraquinone and 1, 4-dihydroxyanthraquinone (quinizarin). Morin is the most sensitive but is less specific than the others. Dr. Neuman has already reported his results with 1-amino-4-hydroxyanthraquinone. Quinizarin, which was mentioned in Public Health Bulletin 181[12] as a suitable fluorometric reagent, was studied carefully by Fletcher, White, and Sheftel[207] for the determination of beryllium in ores. They found that it was the most suitable of the three fluorometric reagents listed in table LXIII and was sensitive to less than 1 microgram of beryllium in 25 cc. of test solution. In tests on beryllium ores they attained a rather high degree of precision for a fluorometric method, as is shown in table LXIV.

Table LXIII. Fluorometric methods

morin
1-amino-4-hydroxyanthraquinone
1,4-dihydroxyanthraquinone (quinizarin)

Table LXIV. Determination of beryllium by fluorometric quinizarin method

	Beryl concentrate (per cent)	*Medium-grade beryl ore* (per cent)	*Low-grade beryl ore* (per cent)	*Tailings* (per cent)
Average value (gravimetric)	11.2	5.51	1.39	0.26
Fluorometric (visual)	11.1	5.36	1.38	0.26
	11.2	5.51	1.39	0.25
	11.1	5.38	1.36	0.24
	11.2	5.36	1.39	0.26

Summary

In summary, we can say that chemical methods have been worked out for determining beryllium in amounts as small as 0.5 microgram. While

methods thus far published are not entirely satisfactory for estimating the minute quantity of beryllium in some kinds of biologic material, it is expected that reliable procedures will soon be available.

Discussion

HERVEY B. ELKINS, PH.D.*

As Mr Durkan has indicated, the analytical chemistry of beryllium, even when dealing with relatively large amounts, is by no means simple We have done some work, with only mediocre success, with some of the separations which he described, using both the oxine method and the ether hydrochloric acid precipitation of aluminum.

We tried out the rufianic acid method (1, 4-dihydroxyanthraquinone, 2-sulfonic acid) as described by Fairhall and his associates The original procedure for this method involved using 1 cc. aliquots out of 100 cc. in the entire sample Since the method is sensitive to only 1 microgram per aliquot, this would mean a sensitivity of 0 1 mg. in the entire sample, which is not very satisfactory. We were able with some difficulty to adjust this method to determine larger aliquots, 5 cc. out of a total volume of 10 or at most 25 cc When we tried this out on air samples, however, we found there were interferences which we were unable to eliminate Separation of aluminum by the methods outlined above was only partially successful, and magnesium also interfered.

We are now working with a morin method using a Coleman photofluorometer This method has some advantages in that reaction is done in strongly alkaline solution, which eliminates a good many of the interferences. We find rather high blank readings, however We have found that a 20 per cent aliquot from an air sample basic blank before the addition of reagent amounts to about the same as the fluorescence given by 1 microgram of beryllium. The blank reading given after the addition of reagent amounts to more than twice the increment caused by this amount of beryllium However, as long as these various blanks are reproducible, we are hopeful of getting some reasonable results.

As you are no doubt aware, in fluorescence work it is very important to

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remove all traces of smoke or oil For this reason, in practice it is necessary to ignite air samples to a red heat in order to destroy any such organic matter that may be present.

As Mr Durkan has pointed out, there are available chemical methods for determining beryllium now to amounts as low as 0 5 microgram An important question which might well be raised at this point is, is this sensitivity sufficient? I do not think that the toxicology of beryllium is as yet well enough understood to enable this question to be answered directly However, if we reason somewhat by analogy of the heavy metals, we may arrive at an answer which, for lack of something better, may be of some value In the case of lead, which has been studied for a good many years, we have long had methods capable of determining quantities of a milligram or slightly less We have also had the spectrograph for some time These methods were, in general, found adequate for evaluation of air samples Only a few laboratories, however, were able to work successfully with biologic materials, especially with human tissues, using these methods When the dithizone method capable of a sensitivity of 1 microgram was developed, however, the number of laboratories which could do this work was greatly increased, and we have, I believe, made great strides in our study of the lead problem by use of this technic

Now if we are to consider that an atom of beryllium is as harmful as an atom of lead, the relative atomic weights must be considered Beryllium with an atomic weight of 9 has somewhat less than one-twentieth the mass of lead, which has an atomic weight of 207 This means that a section of bone or other tissue which contains 1 microgram of lead may be considered as no more abnormal than a similar section containing somewhat less than 0 05 microgram of beryllium In order therefore, to make a chemical analysis of such tissue for beryllium that would be as significant as a dithizone analysis for lead, we need a method which is sensitive not to micrograms but to hundredths of a microgram Such a method does not seem imminent, but there is, of course hope that it will be developed in the near future

CHAPTER 27

Spectroscopic Methods

A POBITSKY*

Early in November 1944, the late Dr Gardner, of the Saranac Laboratory, sent us for spectroscopic examination a sample of lung ash of a person who had worked in a plant in Salem in which fluorescent powder was used. This person had the disease which was then called Salem sarcoid Dr. Gardner was particularly interested in the elements that make up the inside coating of fluorescent lamps. Mentioned in his letter were the elements zinc, beryllium, cobalt, antimony, copper, tungsten, cadmium, and silicon.



FIG 165 Spectrogram of samples of lung ash

We took a few spectrograms of the sample and ascertained the presence of some twenty elements in it, amongst them some of the elements under consideration, namely beryllium, zinc, and lead We had to establish whether or not these elements were normal components of lung ash. We asked Dr. Gardner if he could supply us with a lung ash sample of a person having no known dust exposure He sent us the lung ash of a Norwegian sailor One of this sailor's lungs showed localized tuberculosis and the other one, which was ashed, was essentially normal.

We took spectrograms of the new sample. The ash from the sailor's lung showed no evidence of beryllium or zinc and the lead content was

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low. Figure 165 shows part of a spectrogram of the two ash samples in juxtaposition (the sailor's spectrogram is the upper one and the Salem worker's, the lower one) The elements found in both ash samples are given in table LXV The numbers alongside each element represent relative intensities of the spectral lines and are to be compared with one another in a horizontal direction only (It is easier to bring out the spectrum of some elements) At the top of the table are listed the elements

TABLE LXV SPECTROGRAPHIC ANALYSES OF LUNG ASH

Element	*Sailor A-42-52*	*Fluorescent P-44-322*
Na	100	150
K	75	50
Li	—	3
Sr	3	25
Ba	10	10
Ca	75	100
Al	25	30
Mg	75	75
Si	50	50
P	75	80
Fe	50	50
Mn	2	10
Ti	3	3
Cu	25	25
Ag	1	1
Sn	1	1
Cr	5	0
B	5	0
Be	0	50
Pb	0	25
Zn	3	25

nmon to both samples At the bottom are the elements where differ-
es are present The Norwegian sailor's spectrogram showed small
unts of chromium and boron The Salem sarcoid showed appreciable
nts of beryllium, zinc, and lead, while no beryllium or lead and just
le zinc were present in the Norwegian sailor's ash
communicated our findings to Dr Gardner He told us that the
on of cadmium was brought up We found no evidence of cadmium
spectrograms At the time we did not know whether this element

tends to accumulate in the lungs. Subsequently, we had occasion to examine other lung ash samples that showed evidence of cadmium However, they were not connected with exposures to fluorescent powders

This was probably the first bit of evidence that the Salem sarcoid contained some of the components of the fluorescent powders.

TABLE LXVI. SPECTROGRAPHIC ANALYSES OF LUNG ASH

Element	*Fluorescent P-44-322*	*Fluorescent P-43-297*
Na	150	100
K	50	75
Sr	25	10
Ba	10	9
Ca	100	100
Al	30	30
Mg	75	80
Si	50	55
P	80	85
Fe	50	50
Mn	10	8
Ti	3	3
Cu	25	25
Ag	1	1
Sn	1	10
B	0	5
Be	50	40
Pb	25	50+
Zn	25	25

On December 7, 1944, Dr Gardner sent us the lung ash of another Salem sarcoid, P-43-297 We made a comparative analysis of the two Salem sarcoids (table LXVI) There were minor variations between the two samples but the elements under suspicion were present in both An outstanding point about the new sample was the comparatively high lead and tin content, as if the patient was subject at some time or another to combined fumes of these elements

On January 17, 1945, we received 4 more ash samples. None of these were Salem sarcoids Samples P-40-230, No 0 and No 4, were taken from different parts of the lungs of the same person, a granite driller for ten and a half years His case was marked "Silicosis-sarcoid" and No 4, right upper lung, was marked "Massive fibrosis." Case P-44-326 was

marked "Sarcoid and mild asbestosis, occupation not known except some exposure to asbestos" Case P-44-328 was marked "Sarcoid-like disease very similar to Salem cases"

Table LXVII gives the results of our findings A-42-52 (Norwegian sailor) is included for comparison Only the last of the four cases shows

TABLE LXVII SPECTROGRAPHIC ANALYSES OF LUNG ASH

Element	Norwegian sailor A-42-52	Granite driller P-40-230 No 0	Granite driller P-40-230 No 4	Asbestos P-44-326	Radio tube P-44-328
Na	100	100	50	75	75
K	75	75	75	100	40
Sr	3	3	1	1 5	2
Ba	10	10	5	5	20
Ca	75	75	100	80	70
Al	25	25	20	50	30
Mg	75	75	50	75	60
P	75	75	30	60	75
Si	50	60	50	100	50
Fe	50	60	50	75	50
Mn	2	2	0 1	3	10
Ti	2	3	2	5	2
Cu	25	25	20	25	25
Ag	1	2	0 7	2	3
Sn	1	5	1	3	4
Cr	5	0	1	3	3
B	5	3	3	1	1
Be	0	0	0	0	5
Pb	0	1	1	25	5
Zn	3	2	1	5	2
Bi	0	0	0	10	0
Pt	0	0	3	3	0
Cl	0	0	5	0	0

any beryllium The "mild asbestosis" case, P-44-326, shows the presence of bismuth, a newcomer in the lung ash samples A spectrogram of asbestos taken by us a year earlier shows the presence of bismuth This sample is also rich in lead and silicon

Our next contact with Dr Gardner was about eleven months later. We received two ash samples in December 1945, and two more in January 1946

We detected beryllium in all four samples (table LXVIII). However, a new factor arose to cast uncertainty over the results At the Saranac Laboratory on the floor above the room in which chemical analyses were made, they were *running* an inhalation experiment on animals, which contaminated the air with zinc beryllium silicate. It was subsequently found (by the use of a fluorescent microscope) that there was an appreciable contamination of the atmosphere of the whole building with these phosphors Particles of these materials were settling at the rate of three or four per square centimeter per hour in various parts of the laboratory. It was quite conceivable that the lung ash might have been so contaminated. On the other hand, it is also possible that the four cases had exposure to beryllium compounds.

TABLE LXVIII. SPECTROGRAPHIC ANALYSES OF LUNG ASH

Element	*Mother of employee P-45-358*	*Brass Factory P-45-359*	*Crematory P-45-355*	*Fluorescent P-45-361*
Na	500	500	500	500
K	100	100	85	100
Mg	50	50	50	50
Ca	75	100	75	75
Sr	15	5	15	5
Ba	3	10	5	0
Al	10	12	20	15
Ga	0	0	5	0
Si	50	50	50	40
B	1	25	0	0
Be	25	10	20	30
P	50	50	50	60
Fe	50	50	50	50
Ni	3	3	5	3
Ti	10	5	10	8
Cr	5	5	5	5
V	5	0	5	0
Mn	5	5	5	5
Zn	10	15	65	15
Cu	15	15	25	25
Ag	3	3	1	1
Cd	0	3	10	0
Sn	10	3	12	1
Bi	10	1	0	5
Pb	5	8	30	12

Aside from the question of beryllium there are other points of interest about these samples. This is the first time that we find evidence of cadmium in lung ash samples Bismuth previously found in the asbestosis case is again present here. Boron is present in the brass factory worker in larger amounts than in the case of the Norwegian sailor Gallium is present for the first time, evidently associated with the larger amounts of aluminum

On April 29, 1946, Dr. Gardner found that they had the ash of an earlier case of a Salem sarcoid, P-45-338 The results of our observations are given in table LXIX The sample shows the same general characteristics.

TABLE LXIX SPECTROGRAPHIC ANALYSIS OF LUNG ASH

		Fluorescent *P-45-338*			
Na	500	Be	30	Zn	15
K	75	P	60	Cu	25
Mg	50	Fe	60	Ag	1
Ca	75	Ni	5	Sn	3
Al	15	Ti	8	Pb	10
Si	45	Cr	5		
B	1	Mn	5		

Another case, P-46-369, came up later (August 8, 1946) from a brass foundry Dr Gardner stated: "The tissue looks more like silicosis than it does sarcoid in many places, nevertheless, there are typical lesions of the latter present" Beryllium is present and lead, zinc, copper, silver, cadmium, tin, and boron are present in relatively large amounts (table

TABLE LXX SPECTROGRAPHIC ANALYSIS OF LUNG ASH

		Brass Foundry *P-46-369*			
Ca	100	Pb	30	Fe	100
Al	5	Zn	50	Mn	10
Mg	50	Cu	50	Ti	5
Si	15	Ag	5	V	10
P	50	Cd	10	Ni	3
Na	100	Sn	5	Cr	10
K	100	B	15		
Sr	10	Be	20		

LXX). Dr Gardner seemed to be convinced by then that the presence of beryllium is of fundamental importance.

About two months later I learned the sad news of the passing away of Dr. Gardner.

To obtain an idea of the order of magnitude of the amount of beryllium present in the lung ash, we obtained a lung through the kind offices of Dr. A. D. Nichol. We ashed the lung and then added to two portions of the ash the equivalent of 0 01 and 0.1 per cent by weight of beryllium The original sample was found to contain a very small amount of beryllium, to which we assigned a value of 3 on the previous basis.

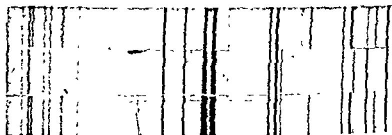


FIG 166 Spectrogram of sample of lung ash compared with control samples containing a known amount of beryllium.

We then took a spectrogram of P-44-322 as well as of the two above treated samples using equal amounts and giving equal exposures in all three Figure 166 shows the spectrogram in the vicinity of the beryllium lines From the relative intensities of these lines we see that P-44-322 (middle) contains more than 0 01 per cent (upper) and less than 0 1 per cent (lower), though closer to the lower one.

Discussion

JACOB CHOLAK*

Mr. Poritsky's paper was very interesting, particularly the spectrograms of lung tissue which clearly show the presence of beryllium in those cases diagnosed as sarcoid due to beryllium exposure This is in complete

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agreement with our own spectrographic experience in analyzing similar material.

The spectrographic method for determining beryllium in biologic material was adopted in our laboratory when a search of the literature led us to the same conclusion expressed by Dr Elkins that the chemical

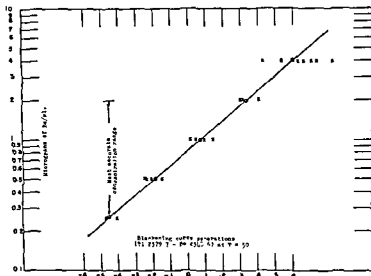


Fig 167 Working curve for spectrographic determination of beryllium

methods currently being used lack specificity and sensitivity Early work indicated that the spectrographic technic was very promising, but that difficulties might be expected in the preparation of the samples for analysis As a result, much of the work was concerned with the development of methods of sample preparation and with the isolation and concentration of minute quantities of beryllium without loss

A satisfactory and precise quantitative method was finally developed. This method[11] will appear shortly in *Analytical Chemistry*, but some of the details will be presented in this paper Before doing so, however, I might add that further work on sensitivity has resulted in such a remarkable increase in the sensitivity of detection that the exacting sensitivity requirements which Dr. Elkins has set for a suitable chemical method are now being met.

Figure 167 reproduces the working curve which is used to evaluate the spectrograms of the samples It was derived from data taken from spectra of solutions of known amounts of beryllium in a buffer solution containing thallium as an internal standard. The curve is shown not only to illustrate the range of analysis and the type of photometry which is employed, but also to demonstrate the effect of "self-reversal." Thus each x mark represents an average value obtained for a set of 6 spectra on a single plate. The straight line passing through the circles is the working curve, and at each point the circle gives the mean value for the total number of spectra taken. The increasing spread of the x values with increasing concentration is due to "self-reversal" of the beryllium line, and this plainly indicates that satisfactory analytical values are obtained only in the range 0 2 to 2 micrograms of beryllium per ml of solution. Higher concentrations of beryllium may, however, be determined if the prepared sample solution is adjusted to a suitable volume. The most sensitive beryllium line at 2348 Å is used since it is the only line that appears with the quantities of beryllium which are likely to be encountered in biologic material.

Since the amounts of beryllium in biologic material may be very minute, an adequate analytical procedure involves the proper preparation of the sample and the isolation and concentration of beryllium without loss. Table LXXI shows how the isolation and concentration of beryllium

TABLE LXXI ISOLATION OF BERYLLIUM BY ENTRAINMENT WITH PHOSPHATE (PRECIPITATION FROM FRESH URINE, 40 ML.)

Micrograms Be added	*Micrograms Be recovered*
0	0, 0
0 5	0 65, 0 60
1 0	1 10, 1 05
2 0	2 0, 2 0
4 0	3.5, 3 5
8 0	8 8, 9 0

are accomplished It may be seen that beryllium is completely removed from solution by entrainment (or precipitation) when a solution containing beryllium is made just alkaline to phenol red and the phosphates of calcium and magnesium precipitate out.

Before this satisfactory procedure for isolating and concentrating the

beryllium can be used, it is first necessary to obtain a suitable solution of the ashed biologic material Table LXXII lists the results obtained with a dry ashing procedure It may be seen that such a procedure is unsatisfactory, since appreciable quantities of beryllium are lost.

TABLE LXXII LOSSES OF BERYLLIUM ASSOCIATED WITH DRY ASHING OF URINE SAMPLES AT 500° C.

Type of dish	*Micrograms Be added*	*Micrograms Be recovered*	*Average recovery per cent*
Glazed silica	1	0 9, 0 4	65
Glazed silica	2	0 4, 1 2, 1 4	50
Glazed silica	4	3 0, 2 2	65
Glazed silica	16	9 6, 2 4	38
Platinum	4	0 5	12 5
Platinum	8	3 2	40

Table LXXIII, shows the results obtained after "wet ashing" the samples. This procedure involves the use of sulfuric, nitric, and sometimes perchloric acids and, as the data indicate, is the preferred procedure

TABLE LXXIII RECOVERIES OF BERYLLIUM FROM BIOLOGIC MATERIAL FOLLOWING WET ASHING

Material	*Grams*	*Micrograms Be added*	*Micrograms Be recovered*
Blood	10	0	0, 0
Blood	10	0 5	0 65, 0 60, 0 60, 0 5
Blood	10	1 5	1 6, 1 6
Liver	10	0 8	0 6
Liver	10	11 5	11 5, 11 0

Although the spectrographic method is specific, a slight interference occurs if large amounts of iron are present. This interference is not one of masking of the beryllium line, but rather that due to "foreign ion effect" In the presence of large amounts of iron, the intensities of weak beryllium lines are enhanced to a greater extent than is the internal standard line, with the result that the quantitative findings for traces of beryllium are in error, being usually on the high side as is shown in table LXXIV The interference by iron, however, may be eliminated easily if the iron is removed with cupferron, as has been suggested by

one of the earlier speakers. That this procedure is effective and does not result in loss of beryllium is also evident from the data in table LXXIV.

TABLE LXXIV RECOVERY OF BERYLLIUM IN THE PRESENCE OR ABSENCE OF IRON (MATERIAL = 10 GRAMS OF BLOOD EXCEPT AS INDICATED)

Micrograms Be added	Micrograms Be recovered	
	Fe Present	*Fe removed*
0	0, 0	0, 0
0 5	1 4, 0 9	0.65, 0 6
0 5	0 8, 0 7	0 6, 0 5
0 5 (10 gm liver)	0 8, 0 6	0 5
1 5	1 7, 1.9	1 6, 1 6

The outline just given covers only the high lights of the procedure, which in summation consists of the following steps:

1. Wet ashing of the sample
2. Isolation and concentration of beryllium by entrainment in or precipitation as the phosphate.
3. Removal of iron where necessary by means of treatment with cupferron
4. Spectrography.

The procedure has proved quite satisfactory in our investigative program and has been used on all types of biologic material and also in analyzing air contaminated with beryllium dusts Although satisfactory for most purposes, this method lacks sufficient sensitivity to determine the minute quantities of beryllium which may be present in the urine of workmen exposed to beryllium dust, particularly since there is considerable evidence that the amount may well be only a fraction of a microgram per liter of urine Since the analysis of beryllium in urine requires a 50 cc sample, the concentration of beryllium which is detectable with the above outlined method is about 4 micrograms per liter Therefore, we have recently reinvestigated the spectrographic technic with the purpose in mind of increasing the sensitivity of detection Remembering that in 1931 Mannkopf and Peters[391] showed how the sensitivity of detection could be increased several fold by employing the "cathode layer" method of excitation, we have incorporated this step

into our procedure. The result has been the development of a method which is capable of detecting 0.003 microgram of beryllium in the arc. The absolute amount detectable, again when using a 50 cc sample, has now been reduced to 0.015 microgram per sample, corresponding to 0.3 microgram beryllium per liter of urine. It is hoped that this newer procedure will permit us to follow the absorption of beryllium by means of urine analysis. Complete details of the more sensitive, modified procedure will be published as soon as possible.[125]

Further Discussion

MR. KJELLGREN: I would like to bring to your attention the peculiar properties of some beryllium compounds. Basic beryllium acetate is very volatile, is sublimed without any loss, and is soluble in many organic liquids. In analytical work the beryllium content, if present as basic acetate, may easily be lost by heating. I should think it would be very interesting to study the beryllium acetates and some of the related organic acid beryllium compounds and their effects and behavior in the body.

I would also like to mention a peculiar property of beryllium sulfate. If aluminum sulfate is dissolved in water, it hydrolyzes slightly and will, therefore, dissolve a small amount of aluminum hydroxide. Beryllium sulfate, when dissolved in water, also hydrolyzes to some extent and it would, therefore, be expected that the solution would dissolve only a small amount of beryllium hydroxide. However, it has been found that beryllium sulfate solutions dissolve very large amounts of beryllium hydroxide, in fact, normal beryllium sulfate may dissolve several equivalents of beryllium hydroxide. The solution, therefore, acts as an acid. I believe this peculiar property should be kept in mind when the effects of beryllium sulfate on the lungs and in feeding experiments are studied. Possibly, after rats had been fed with beryllium sulfate saturated with beryllium hydroxide instead of the normal sulfate, a different result might have been obtained. Also a better conception of the effect of beryllium sulfate in the feeding experiments might have been reached if beryllium sulfate had been compared directly with aluminum sulfate.

As I am probably the only beryllium production man present at this meeting, it may be interesting to you to know what the operators in a

beryllium plant are afraid of and what they are not afraid of. We are not afraid of beryl ore, beryllium oxide, beryllium copper, or other alloys, or of beryllium metal itself. We are afraid of beryllium metal dust and dust of beryllium sulfate, beryllium fluoride, beryllium chloride, and beryllium copper dross

I know this viewpoint is very unscientific, but I think it may be of significance, as it has been developed from years of experience. I leave it with you for what it is worth.

Another thing that I would like to mention again is that we worked with beryllium in our plant for five years before we had any case of acute pneumonitis During this period we were all exposed to beryllium-containing dusts in the form of silicate, sulfate, and oxide No explanation of this effect has come forward in this meeting Somebody suggested that the reason may be found in a change of the composition of beryl ore which, during this period, was mostly purchased from India and the United States. The main source of beryl ore is now Brazil. Another explanation that has been suggested is that our plant operators were all immune during this early period and that we later began to employ people sensitive to beryllium compounds I do not think that any of these explanations is satisfactory

DR KLEMPERER I was particularly interested in the data Mr. Kjellgren gave us on the chemistry of some of the beryllium compounds As you have heard, the literature is almost devoid of description of the chemistry of beryllium, in textbooks, it is usually treated in small print. We have data about a few of its reactions, but we know little about the physical properties of the salts

More knowledge about organic compounds, undissociated inorganic compounds, etc , might help us not only in developing methods, but also might give us an understanding of various phases of the disease in case the basic agent is not the beryllium itself but some compound which does not readily dissociate within the body.

So, any kind of information from people who know more about the chemistry or physicochemistry of beryllium can give us added knowledge about the physiologic implications We more than welcome such information

DR. VORWALD Are there any other questions from the floor?

DR MARTLAND· For the record, I would like to clear up a statement by one member that the amounts of beryllium found by the Kettering Laboratory in one of my chronic cases were in hundredths of a microgram (an exceedingly small amount)

Without again showing the table of analyses, unless you request it, the column referred to represented a conversion of micrograms into milligrams

DR VORWALD If the member who put the question some few days ago wishes to comment, please do so

DR KLEMPERER It satisfies me completely When I referred to the third decimal, I did not mean three decimals after the point, but three decimals whether to the right or left of the point

A Further Program

WILLARD MACHLE, M.D.*

The problem with which we are dealing carries with it a great responsibility. By concerning ourselves with the beryllium problem, we take upon ourselves indirectly the responsibility for the health of the thousands of workers who are now exposed to this element.

With due regard to the combined efforts of all concerned, it should be stated that we are all attempting to get in a few years time knowledge of a disease that normally would be accumulated only after decades of study. Silicosis has been known for years, yet knowledge of the mode of action of the various forms of silica and the treatment are today still far from clear. Even though a concerted and systematic series of research enterprises are carried out by all, and if these are coordinated and integrated to obtain the maximum saving of time and effort, we still have no assurance that a practical answer to this problem will be written before many years have elapsed. In the meantime, we must concern ourselves with prevention, since this remains the best treatment, and continuing efforts must be made to reduce exposures in plants to as low a level as is economically feasible to achieve.

I should like to review briefly where it seems to me that we now stand with respect to information on certain aspects of this problem and what we need to do and need to know to get a little farther along with our understanding.

It is obvious from the complexity of the problem which has occupied the interest of a number of people for four or five years that it is not one that will readily be solved, nor is the problem one that is likely to lend itself easily to solution by any intuitive or direct approach. Prac-

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tically all of the tools and scientific disciplines that we have must be utilized on this problem if we are to have any hope of unraveling it

It was pointed out by Dr Elkins a little earlier that we stand now with respect to beryllium analyses where we stood with lead analyses twenty years ago We also stand now with respect to clinical observations of beryllium intoxication where we stood many, many years ago with lead The same approaches and the same technics will have to be used, but these must be compressed and accelerated in order that we may define the clinical entity and determine the course and characteristics of the disease, all of the initial effort being directed toward the protection of the large number of people who are now in a state of jeopardy of undetermined magnitude

The research method usually begins with definition of the problem and some very serious attempts to do this have been made at this meeting and earlier

In dealing with diseases of occupational origin, one usually next begins with the epidemiology. Where does the disease occur, what is its characteristic distribution, and what is its relationship to the many variables associated with exposure? In the last year and a half, much of the epidemiology has been clarified A number of cases have been reported from a large variety of industries, all having potential exposure to beryllium There has been exposure to beryllium metal, beryllium oxide crucibles, in the manufacturing use of phosphors, in laboratory work with beryllium, and elsewhere While the pattern of distribution of disease from this exposure indicts beryllium almost without question as the cause of the acute and chronic diseases that we are talking about, yet these are not proven sources in the strictest sense because we do not as yet have a tool with which to characterize either the exposure or the quantitative relationships of beryllium in the body

The recent improvement in spectrographic analytical methods for beryllium have enabled us to collect analytical data on individuals who have died from the disease These cases are clinically, pathologically, and roentgenologically more alike than different, although it must be recognized that there are no absolute criteria for the diagnosis of either the acute or the chronic condition In these cases, all of whom had beryllium exposure, one regularly finds beryllium in the lungs and usually in the other tissues of the body In this series, now totalling 11 cases, beryllium

has been regularly found in the lungs in amounts ranging from ten or twelve micrograms per hundred grams to a hundred or more micrograms per hundred grams of lung tissue.

This association of work and exposure to beryllium—the occurrence of disease and the later finding of beryllium in the tissues of the organism—does not necessarily establish cause (if we use the phantom word), but it does establish relationship. These cases were all exposed to beryllium, and it is true that to date lungs and bones have been free from beryllium where there has been no exposure and death has been from other causes or diseases. We will, however, need a large number of analyses on people who work with beryllium from day to day and who die accidental deaths or from other causes in order to establish the order of magnitudes of beryllium deposit which can come about from exposure alone and not result in the production of disease.

Another important point for future work is to study those situations where beryllium is used and where no cases have been encountered, and there are a number of such. We need clinical and epidemiologic studies in order to find out what magnitudes of exposure and types of compounds are involved in these situations where there has been no disease despite years of exposure.

We further require some mechanism for exchange of information, a central agency for exchange of mortality and morbidity data, case records, and pathology. There is a hopeful likelihood of the Public Health Service interesting itself in this undertaking if only to the extent of offering advice and assistance in coordination of the problem, which has now spread widely throughout American industry.

Further clinical studies will have to be carried out on all available cases. The disease requires characterization and attempts should be made to set up definitive diagnostic criteria. There has been great progress made in this direction, but one now needs clinical studies associated with chemical studies which will not only assist in the characterization of the disease but possibly enable us to establish an etiologic diagnosis.

If we are going to assume, as we do, that beryllium is associated with the production of this disease in one way or another (and I, at least, am convinced that it is), it should be possible to do certain things We should establish its presence and distribution as an element in the organism suffering from the disease. If an element is responsible, one

should be able to use the measurement of metabolic relationships of the element in the same way that has been done with lead and arsenic. We must relate the amounts coming in, the amounts present in the organism, the amounts leaving and the equilibrium level

And then more importantly perhaps—because after all, our concern is with the people who are working, and the safeguarding of operations—if an element is concerned, it should be possible to define the relationship between levels of exposure present in the air and the equilibrium level present in the organism and again relate these levels with the appearance or nonappearance of disease

The business of characterizing all of these things is dependent upon a satisfactory analytical method.

I think this symposium has been a very happy occasion for many of us We have heard reported for the first time now, an analytical method which will give us a working tool both for plant control and for the characterization of the disease as well as for the control of animal experimentation

The requirements for an analytical method have been well defined by Dr Elkins and others who have spoken The requirements are determined by the quantities you will encounter in conditions under study That was not too well thought through at the outset when attempts were made to devise methods Attempts were made to adapt methods to use rather than to define quantitatively the problem as it actually existed

We heard today of spectrographic methods satisfactory in dealing with particular amounts of beryllium

One point I want to bring out with respect to research on analytical methods The history of lead and other analytical methods applied to biologic use shows that in a number of situations, understanding of the problems of the disease were held back because of failure to coordinate results and methods and to exchange samples and standards

History is repeating itself again in the case of radioactive iodine and it is important that there be a continual exchange of samples and a standardization of methods going on in the early developmental work with beryllium Forewarned by the errors of many persons who, working by themselves, published results which later were not comparable because they were obtained by dissimilar methods, we ought not to let that situation occur in this problem

In respect to animal experimentation, I think we have some very hopeful signs that the disease can be reproduced, supplying another link in the development of the role of beryllium. I think the report of Dr Vorwald was highly significant from that point of view. It was particularly interesting that the Grade Four, or the grade just short of what would indicate the pathologic human entity, could be approached by a phosphor of 2.3 per cent beryllium. Certainly these quantitative relationships should be worked out because there are thousands of people working with phosphors with that percentage of beryllium.

The tumor problem has been reported formally in the literature by Dr. Gardner. It is discussed from time to time, and it is a problem I think merits very serious consideration. The startling uniformity with which sarcoma can be reproduced by a variety of beryllium compounds in one species of animal is a significant observation. I think it is not only significant, as pointed out this morning, from the point of view of carcinogenesis, but it is significant to all of us—we are again in a state of unknown hazard with respect to the human population We do not know what will happen ten, twenty, or thirty years hence It took nearly seventy-five years to establish the carcinogenicity of chromium and nickel

I am not unduly concerned with results from one species only, but when one gets clear-cut evidence of the capacity of an element to do certain things, one cannot ignore it, and there must be extensive and systematic research carried out on that particular attribute

In one company there were no cases of granulomatosis in any individual who began work since October 1942, that is, work with lamp phosphors We are recently able to reaffirm this point, since we have found that 2 or 3 cases that were difficult of explanation now can be related to exposure to beryllium in the manufacture of radio crystals, a thing which goes on practically everywhere and no one thinks very much about

One final word on plant control. The air sampling methods, using samples collected by conventional technics, have given us results of the order of magnitude of a tenth of a microgram per cubic foot of air. A series of 52 samples of powder from a phosphor manufacturing plant contained a minimum of 0 09. The particle size of the phosphors is of the order of 0.1 to 0 2 micron.

Many factors must enter into the study of plant control—the particle size, distribution of the beryllium compounds, and the method of preparation Since we have plants in the United States where 2, 4, or 5 per cent beryllium phosphors have been used over a period of years without occurrence of cases, it becomes very important that these plants be studied carefully, using standard methods of collecting samples and reporting results, so we can develop a meaningful threshold of safety in establishing plant control.

Discussion

HAROLD C HODGE, PH D *

The summary of existing knowledge has been so clearly described by Dr Machle that I wish only to underscore what might be called headlines from Dr. Machle's presentation Broadly stated, the principal problems seem to revolve about the necessity of establishing the relationship between the environment (exposure) and the patient (illness) Dr. Williams and Dr Vorwald also have stressed this need.

The first point might well be *the need for a simple, reliable, and accurate rapid analytical method for beryllium* (Dr Nickson emphasized this point) Blood and urine samples, the dust samples from industry, and the tissues of experimental animals at present may be analyzed only by those who have the spectroscopic facilities available Acquisition of a number of control spectrographic analyses is needed on (1) persons with no history of beryllium exposure, (2) persons in related industries (alloys), and (3) persons working with other metals, such as zirconium, titanium, etc Only after such analyses are obtained can proper evaluation be made of positive findings in beryllium-exposed individuals

The second might well be *the need for greater knowledge of beryllium dusts* Is there a special molecular species which produces the remarkable changes observed, or will any beryllium compound provoke this response? We need exhaustive studies of the dusts as to particle size, surface area, shape, hardness, history (for example, conditions of calcination), and source

* Head, Biochemistry Section, Division of Pharmacology, Atomic Energy Project, Professor of Pharmacology, School of Medicine and Dentistry, University of Rochester, Rochester, New York

The third point might be *the investigation of the chemistry and biochemistry of beryllium* Both Dr. Klemperer and Dr. Dill cited numerous deficiencies in our knowledge. With physicochemical technics we would seek solubilities (for example, that of beryllium phosphate) and solution properties, from which the identification of the ionic form in which beryllium exists in the body might be made. The biochemical attack might profitably be centered on the metabolism of beryllium, studies of the beryllium protein complexes, and of the effect of beryllium on cell systems. After Dr. Martland's and Dr Scott's reports we would like to have information about the nature of the inclusion bodies they described

As the fourth item, *the essential character of beryllium as a "necessary and sufficient" condition in the various forms of illness of beryllium workers* should prove a fertile ground for investigation The following questions suggest lines of attack.

Does a metal fume fever follow certain beryllium exposures?

Do the dermatitis and the ulcer differ from somewhat similar injuries found in other exposures, for example in the chrome industry?

Has the osteogenic sarcoma of Gardner been reproducible?

Are the nasal pharyngitis and bronchitis different from those observed in chemical industries where no beryllium is used?

Does the acute pneumonitis follow a pattern never seen except with beryllium compounds? Kawecki suggested that titanium and zirconium might produce similar illnesses.

Is the pulmonary granulomatosis sufficiently characterized? Records are needed of all the minutiae, all of the uses of beryllium need to be investigated, the amounts of these compounds, the kinds of exposures, and details about chronic illnesses in every such industrial exposure brought together

The fifth item centers on the question, *is beryllium plus something responsible?* If we write this as an equation. Be + X factor→disease, the case when X equals zero would be interpreted that beryllium alone, regardless of other circumstances, produces the disorder. When X equals one, Gardner's "necessity" factor would be indicated, from the suggestions at this meeting, such a necessary factor might be fluoride exposure If X is multiple (more than one) then the problem becomes complicated indeed If many factors are involved, dozens of combinations of imbalances might be equally potent in producing disease. In laboratory tests,

perhaps ill effects will only show up in animals under "physiologic stress" Examples of such stress might be found in patients with allergies, pregnancy, infection, debilitation, or injury

The sixth item might well be *studies of the patient* Dr Shipman has called for tests suitable for detecting borderline cases Dr Wilson has pointed out the importance of getting at subclinical, early involvement Special procedures might well be developed for the chronically ill patient to help control cough and secondary infections, to improve the appetite Dr Carmody has pointed up this aspect by suggesting that the patients and the laboratories should be brought together Another aspect of the problem and one that would be invaluable to industry is the desirability of finding a reliable index of susceptibility of new workers to poisoning. A somewhat different aspect of the problem, but to my mind a related one, is the description by Dr Harrington of the benefits which will result from "good metallurgical control"

The final and seventh item which I wish to present is *the study of the possibility of a trigger mechanism* This study would be a fundamental one based on the premise that there are probably only a limited number of reactions which the body is capable of undergoing One would attempt to find out what reaction or reactions it is that beryllium triggers. From the currently recognized responses to beryllium, such as calling forth monocytes, fibrous infiltration, the necrosis in the presence of a high concentration of beryllium, some suggestions as to further experiments may be made Are these, and other manifestations perhaps now only partially recognized, the visible results of a fundamental derangement occasioned by beryllium?

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CHAPTER 29

Conclusion of Sessions on the Beryllium Problem

B. L. VOSBURGH, M.D.*

The beryllium problem presents a new and unique industrial disease, one that is often insidious in onset, baffling in nature, and probably destined to be difficult to control It is a disease affecting primarily the lungs. The acute and chronic forms are doubtless varying manifestations of the same disease.

Beryllium appears to be the most important causative factor or noxious agent in both cases. Beryllium and its compounds should be considered potentially dangerous, but they are too important to industry to be cast aside lightly for fear of health implications. It is unlikely that harmless substitutes will be readily found, but they should be looked for.

Safe methods for handling even Harrington's industrial alloys† must be devised!

Most of the clinical manifestations of the disease are pretty well explained in terms of the physiologic studies that indicate rather clearly a slowed oxygen diffusion rate at the alveolar membrane, a finding readily understood when one views the microscopic lung sections which show thickened edematous membranes and contracted arterioles The exact reason for this thickened alveolar membrane is not well understood. It is without precedent and defies analogy.

The very irregular incidence of cases in the fluorescent lamp industry implies great variation in susceptibility. That factor will make it all the more difficult to prescribe threshold values for exposure.

Experimental work at Rochester, as of July 15, 1947, demonstrates clearly the irritative and destructive qualities of most beryllium compounds, leaves some doubt concerning the toxic properties of beryllium

* Medical Director, General Electric Company, Schenectady, New York
† See Chapter 2, Discussion. (*Ed.*)

metal and its oxides, simulates some clinical findings, almost duplicates acute beryllium pneumonitis, but admittedly fails to actually do so. And we can add that the workers at Saranac Lake have almost duplicated the chronic type of the disease, with its classical granulomatous lesion.

There is great promise that a precise and easy analytical method will be given to those interested in the beryllium problem in the near future, and there are fond hopes that tracer studies will afford a better understanding of what happens to beryllium in the organism

If tracer studies show that this metal eventually concentrates in bone, then we may pessimistically expect, from work with rabbits, that some day, years hence, some of the human beings who have beryllium concentrated in their bones will develop malignant bone tumors. This is by no means a pleasant prospect and should be disproved as soon as possible

I read the other day a paper by Carl Dragstead on "Idiosyncrasy to Drugs" and was reminded, at its conclusion, of the beryllium problem He had written a parody which certainly seems to apply here

Build me newer molecules,
Oh, my Soul—
As the swift seasons roll
Let each new compound,
Safer than the last,
Avoid the reactions observed in the past
Till all at length are free
From vexing idiosyncrasy

PART SIX

Shaver's Disease

CHAPTER 30

Clinical Aspects of Shaver's Disease

A R. RIDDELL, B.A , M.B , D P H.*

A report on this condition by Dr Shaver and me was published in the *Journal of Industrial Hygiene and Toxicology* for May 1947 I think that report covers the situation pretty fully up to the time when it was issued It would seem unnecessary to repeat everything that was written then I shall, therefore, confine myself to certain points regarding the disease, with illustrations of special cases

The disease was discovered—as far as its recognition on this continent is concerned—by Dr Shaver, the "father" of the disease. When cases first came to his notice, he was quick to realize that they presented something unusual He soon suspected an industrial relationship. His insistence that these cases were of occupational origin finally led to an investigation which has established the accuracy of his conviction

A medical survey on the employees of the several plants involved was instituted At the conclusion of the survey the cases found were classified according to certain changes demonstrated by X-ray films, prepared on the workers concerned These cases were designated as "early" and "well established" At that time there were 12 of the former and 23 of the latter, and in addition there were 13 films on which we hesitated to commit ourselves, these were classed as doubtful A recent review indicates that there are now 30 cases of "well established" disease, 29 classified as "early," and 17 "doubtful" This apparent increase is partly accounted for by the discovery of additional cases through periodic examination with X-ray, and by extension of the disease in certain instances On the basis of the numbers employed (344) at the time of the survey it would appear that roughly 17 per cent of those in exposure have been affected

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The workers who develop the disease are engaged in the processing of bauxite for the manufacture of corundum. This is effected by heat treatment in special furnaces of the electric type. These furnaces consist of large metal kettles They are fitted with movable electrodes which can be raised or lowered as required They are arranged in rows along the

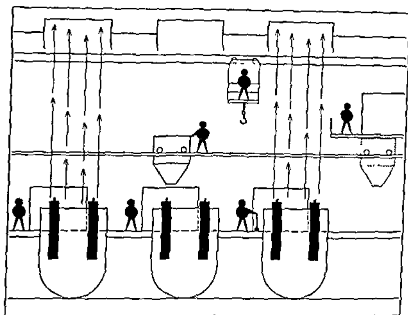


Fig 168 Diagram illustrating the position of the exposed workers in relationship to the furnaces, the storage bins, and the crane

furnace rooms and are fed from platforms situated at suitable levels to allow the furnace tenders to shovel the material into them A certain amount of material is added to the furnace. The electrodes are then lowered and the current applied. The heat generated by the electric arc fuses the material. From time to time during the operation further material is added. During the fusion, and particularly when additional material is added, a dense white fume is evolved from the surface of the furnaces Although most of this fume is carried upwards by the heat draft to escape through openings in the roof, much contamination of the atmosphere in the neighborhood of the furnaces occurs The fume contains considerable quantities of alumina and silica and small quantities of many other substances In certain of these plants methods for the removal

of the fume have been devised, and this has materially reduced the contamination of the atmosphere in the neighborhood of the work places In one installation the improvement is very marked Some difficulties have been encountered, however, and some time may elapse before the installations are satisfactorily completed

The disease which sometimes follows the inhalation of this fume is essentially a lung fibrosis It develops gradually in the majority of cases, but in certain instances disturbingly rapid development proceeding often to gross involvement of the lung structures has been noted Spontaneous pneumothorax, often bilateral, is a special feature of advanced cases and this was present in each of the known fatal cases

There are no characteristic symptoms Symptoms are apt to be surprisingly meager when compared with the evidence of disease indicated by chest films Most "early" cases are symptom free. A few complain of mild dyspnea, which in most instances is present for considerable periods of time before it attracts much attention In "more advanced" cases relatively slight dyspnea is apt to be interspersed with periods, generally of sudden occurrence, when dyspnea is extreme This is often associated with chest pain which may be severe. When these attacks of dyspnea and/or chest pain occur it is evident that the patient concerned has developed spontaneous pneumothorax

Physical signs are absent in "early" cases In the "more advanced" cases these are varied Loss of weight and strength, frequently contributed to by loss of appetite, are common The chest findings to be elicited on physical examination depend largely on the degree of lung involvement, the presence of pneumothorax, and the distortion in the structures related to the chest

It is evident that diagnosis depends largely on the chest radiograph and in this connection I wish to emphasize the necessity for films of good quality This is particularly important in the early stages. It may not be quite so important when the condition is advanced For situations like this the use of portable apparatus is apt to be very confusing, as such equipment does not, as a rule, produce films in which the finer changes can be appreciated.

Figure 168 illustrates diagrammatically the arrangement of the furnaces in a furnace room Although it is out of proportion it indicates the position of the platform and the feeders who tend the furnaces. Bins are

situated behind each furnace. The arrangement of the distributing carriers can be appreciated In one plant the main storage bin is situated above the furnaces. In each plant cranes situated high up in the furnace rooms are used to shift the kettles with their fused material It is in

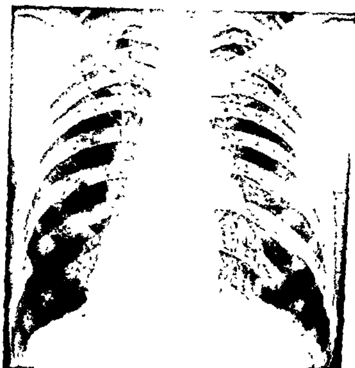


FIG 169 Chest roentgenogram of a 30-year-old worker exposed for 8 years It exhibits unusual shadowing and a peculiar ringlike shadow on the right side There is also a small pneumothorax on the right.

these several positions that the main exposure occurs and where the operators are affected.

A table[552e] previously published refers to the "well-established" cases originally discovered The first five cases and cases 8, 9, and 12 should be specially noted as I shall refer to them presently. I would like you to note the number of persons listed as reacting negatively to tuberculin In several of these cases, particularly in Case 5, the red blood count was high Vital capacity readings, where these have been listed, are of interest. In certain of these cases the vital capacity is now considerably lower

than listed. The date of death in Case 2 is incorrect This man died on May 25, 1943, and not in November as indicated Case 9 has died since the table was prepared.

Figure 169 is from a film, prepared in February 1942, on the first case



that came to Dr Shaver's attention The patient was a young man, 30 years of age, who had been eight years in exposure He was referred for examination because he had developed sudden, severe chest pain after unusual exertion The film exhibits unusual shadowing and contains a peculiar, somewhat ring-like shadow suggesting, somewhat, cavity formation on the right side It also exhibits a small pneumothorax There was considerable discussion as to the nature of the condition. Tuberculosis

was considered but the patient did not react to tuberculin even when this was repeated in increased dosage, and he was not ill. After a period of rest he returned to work, but his occupation was changed. A film, prepared in March 1942, showed the same general characteristics, but the ring-like shadowing had changed. A lateral film prepared about the

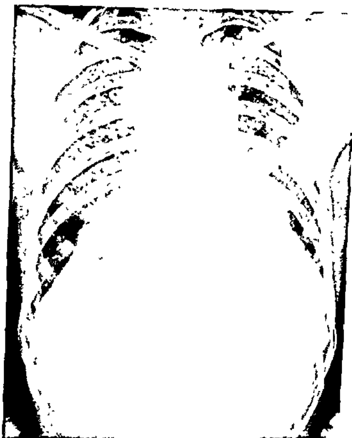


Fig 171 Chest roentgenogram of a man, 25 years of age, exposed for 62 months as a furnace operator.

same time indicated that the ring shadow was situated in the neighborhood of the interlobar fissure. It was evidently part of the pneumothorax. Later films indicate that the pneumothoraces have cleared and there has been no significant change in the general lung shadows (fig 170). The patient has remained in good health and is still at work.

Figure 171, prepared in August 1942, is from a man 25 years of age He was a furnace operator and had been sixty-two months in exposure, When first seen he gave a history of progressive dyspnea, irritating cough with whitish sputum, and considerable loss of weight Because of these symptoms he had left the plant in 1941 and attempted work for a few



Fig 172 The above case (fig 171), 7 months later The film indicates the appearances common to well-established cases peculiar lacelike lung shadows, pneumothorax, distortion of the diaphragm, and widened mediastinal shadow

months as an electrician During the winter of 1941 he experienced sudden chest pain which was severe for two days and then gradually became less acute The period of severe pain was accompanied by very marked

dyspnea. During this young man's illness he was seen by several consultants who made various diagnoses

Figure 172 is also from this case It was prepared in March 1943. He was finally admitted to the Toronto General Hospital on May 23, 1943. On the 24th, he suddenly became extremely dyspneic with rapid respira-



Fig 173 Chest roentgenogram of a man, age 32, with 36 months exposure, exhibiting pneumothorax and fluid The fluid subsequently disappeared.

tions and marked cyanosis In spite of the administration of oxygen and other measures for his relief he died on the 25th. Until the time of his death no definite diagnosis had been established. It was, however, suggested that he had suffered from some form of silicosis These films indicate the appearances common to well-established cases. You will note the widening of the mediastinal shadow, the distortion of the diaphragm, the peculiar lace-like lung shadowing, and the pneumothorax It should

be observed that the shadowing, unlike that common to beryllium cases, is not pronounced in the lower portions of the lung fields This case, following on his first case, arrested Dr. Shaver's attention and made him suspicious of an occupational background



FIG 174 Chest roentgenogram of a man, age 40, with 29 months exposure

Figure 173 is from a man 32 years of age, who had had thirty-six months exposure He had been apparently well up to July 1942, when he began to notice shortness of breath He continued at work, however, until February 1943, when he had a sudden exacerbation of symptoms He never experienced violent pain but suffered considerable chest discomfort and dull chest pain during most of his illness He was admitted to the hospital and was thought to be suffering from some form of pneumonia He may have had pneumonia at that time, because it is evident that the

symptoms in some of these cases are precipitated by attacks of pneumonia. It is also evident that at times pneumonia occurring in an early case will be followed by a blossoming out to a full-blown, well-established case. It should not be difficult to determine whether the pneumonia is real or not. When a patient with an elevated temperature is admitted to

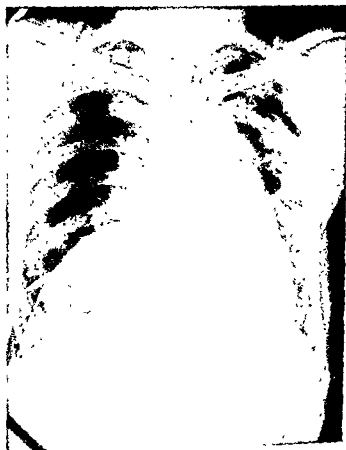


Fig. 175 The above case (fig. 174), 11 months later, at which time bilateral pneumothorax, extensive collapse of the right lung, and mediastinal shift to the left were noted

the hospital and has clinical signs of pneumonia, the condition should be clear. If, however, there is no elevation of temperature, pneumonia is unlikely. This film illustrates what occasionally occurs in these cases. You will notice the pneumothorax and the evidence of fluid. It is of interest that in every case where fluid was noted, it disappeared without

interference and it has never become infected After his discharge from the hospital he attended various clinics, at one of which a diagnosis of tuberculosis was made He then came under Dr Shaver's care in the sanatorium Investigation indicated that he did not react to tuberculin and observation failed to show that he was tuberculous He left the sanatorium

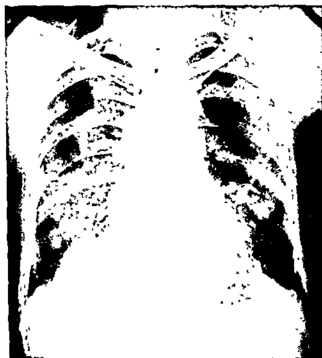


FIG 176 Same case as above (figs 174 and 175), but some 3 years later than fig 175 Extensive pulmonary pathology with extreme emphysema and distortion are now evident

against advice and returned home. After several remissions and exacerbations of his symptoms he died in January 1944 An autopsy was obtained

Figure 174 is from a man 40 years of age, who had been twenty-nine months in exposure He was first sent to Dr. Shaver for examination in July 1943, because of difficulty in swallowing Spasm of the esophagus was diagnosed. The chest condition was discovered incidentally through

the preparation of a chest film. The patient was referred for treatment and the spasm was relieved After two months' rest, he returned to work in the plant but was removed from exposure. Later in 1943 he left the plant because of illness, complaining at the time of shortness of breath and tightness in the chest. In February 1944, he experienced sudden,



FIG 177 Chest roentgenogram of a man, 40 years of age, exposed for 31 months The film illustrates the X-ray characteristics typical of the disease in advanced stage

severe chest pain with extreme breathlessness This was so marked at the time that he was unable even to walk

The next film (fig 175) was prepared in June 1944, when he was reexamined What had occurred is evident. The film, as you see, exhibits bilateral pneumothorax with more extensive collapse on the right side and the mediastinum shifted to the left The large bleb on the surface of the right lung is particularly interesting as it suggests the probable mechanism of these pneumothoraces.

Following this occurrence his condition gradually but materially improved and he obtained employment as a janitor. He was unable, however, to handle this work for long and finally became unemployable

Figure 176 shows the condition of his chest more or less as it is at present When I last saw this man, he was seriously ill He looked miser-

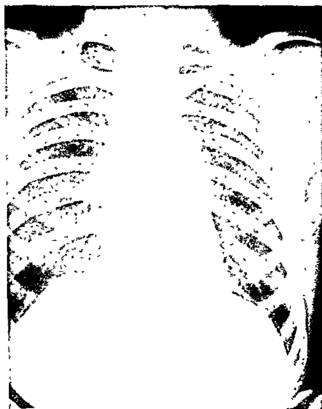


FIG 178 Chest roentgenogram of a man 40 years of age taken on a routine plant survey The widening of the mediastinum portends development of the disease

able and was extremely short of breath, even at rest. He had lost considerable weight The percussion note was hyper-resonant over most of the chest with impairment towards the right base. Breath sounds were almost inaudible Here and there fine, crackling râles were heard There

was no elevation of temperature. He reacted negatively to tuberculin I would like you to notice the profound lung changes indicated by the shadowing and particularly the evidences of extreme emphysema together with the distortion of the diaphragm and other structures. I am informed by Dr Shaver that during the recent summer this man's con-

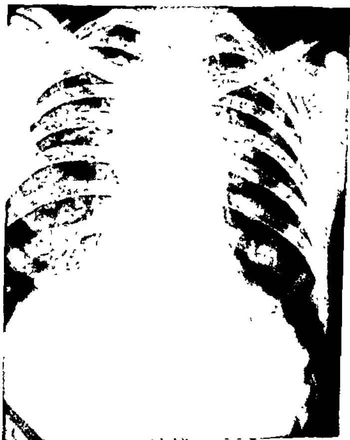


Fig 179. Chest roentgenogram of the above case (fig 178), 1 year and 7 months later Extension of the disease is evident

dition improved considerably, so that he was able to walk moderate distances and even to climb a slight hill He is, however, again beginning to slip

The next film (fig. 177) is from a man 40 years of age, who had been thirty-one months in exposure. Unfortunately, we have little clinical in-

formation respecting this case The present film was prepared in June 1944 It would seem that two or three months before it was taken he had been admitted to a general hospital suffering from what was said to be pneumonia He was apparently admitted to the Niagara Peninsula Sanatorium during Dr. Shaver's absence and he died shortly after admission



Fig 180 Chest roentgenogram of the same case (figs 178 and 179), 2 years and 7 months after the first film (fig 178) The patient expired 5 months later

This is the individual previously referred to with a red blood cell count of over 7,000,000 The relation to the marked lung involvement is interesting He also had a very limited vital capacity. The film illustrates very clearly the X-ray characteristics typical of this disease in the advanced stage

Figure 178 is from a man 40 years of age whose condition was dis-

covered on the plant survey. When first seen he denied symptoms although he later admitted some slight shortness of breath on exertion. His general condition was good Aside from the X-ray findings the investigation was essentially negative. The radiograph was prepared in August 1944, and I must admit its significance was at first overlooked,

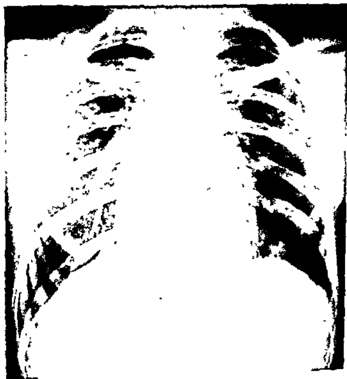


Fig 181 Chest roentgenogram of a man 25 years of age exposed 6½ years, then removed to a non-dusty occupation The roentgenogram reveals thickening of the mediastinum and infiltration throughout both lungs.

because when the survey films were originally examined we did not appreciate the importance of the widening of the mediastinum which is evident here You will observe that there is little distortion of the diaphragm This man continued at work but during most of the remainder of 1944 he was conscious of increasing shortness of breath, together with some cough and expectoration. In March 1945, his symptoms became more marked and in December of that year he suddenly developed left-sided chest pain, together with increased dyspnea. He

was then off work for some weeks but later returned to employment in the plant yard

He was re-examined in March 1946 (fig 179), when he had been off work for some considerable time and his symptoms were severe. He was markedly dyspneic and had lost weight You can appreciate the extension

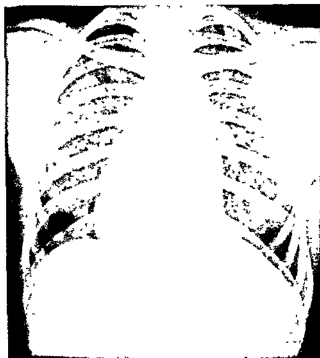


FIG 182 The same case as above (fig 181), but 8 months later The roentgenogram reveals extension of the pulmonary process

which has occurred in the disease and should notice the marked distortion of the mediastinum His chest was well formed, but on respiration the accessory muscles were violently employed and there was indrawing of the lower intercostal spaces The percussion note was generally impaired and the breath sounds were distant. A few crepitant sounds were heard in the upper portion of the chest on both sides

He was re-examined (fig 180) in March 1947, and died on August 15 of the same year An autopsy was obtained

The next two figures indicate the progression which has occurred in another case discovered at the original survey. The first film was prepared in November 1944 This employee was a young man 25 years of age, who had been six and one-half years in exposure. On the basis



FIG 183 Chest roentgenogram of a man 42 years of age employed as a furnace tender for 36 months There is pronounced mediastinal thickening and distortion, diffuse infiltration of the lungs, and pneumothorax. *Death followed 1 year and 7 months later.*

of the X-ray findings his work at that time was changed, but he continued in employment

The case was reviewed in September 1945 (fig 181), when he informed us that late in 1944 he had experienced a violent pain on the left *side of his chest during a spell of coughing He stated that the pain was* severe for three days and during that time he was very short of breath It then gradually subsided and he became less breathless. He continued in intermittent employment until March 1946, when he finally had to stop work.

The next figure (fig 182) shows his condition in May 1946 At present he is in fair condition only. He has lost some 10 lb in weight. He breathes rather rapidly and his heart rate is accelerated His vital capacity is 2000 cc. There are no striking physical findings The note is hyper-



FIG 184 Photograph of gross sections of the lung from the above case (fig 183) Pigmentation, irregular areas of fibrosis, subpleural emphysema, and thickening of the pleura are evident

resonant on the left and the breath sounds are distant especially on that side.

The next figure (fig 183) is from a man 42 years of age, who was a furnace tender for thirty-six months He stopped work in December 1943 His case during his period of illness exhibited the same general features as those disclosed by many of these cases He died in July 1945. An autopsy was obtained and the specimen was referred to Dr Gardner for examination This case is included because histologic sections indicating the pathology of the condition were obtained from the case While

the man was living a diagnosis of tuberculosis had been made, but tuberculosis was not found to be present at autopsy.

Figure 184 is a photograph of gross sections of portions of the lung from the case. You will note the irregular areas of fibrosis, the pigmenta-

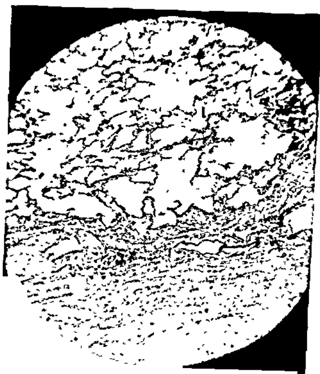


Fig 185 Note the thickened pleura and distortion of the underlying pulmonary parenchyma of the same case (fig 183).

ion of the glands at the lung root, the areas of thickened pleura with leb formation, and the marginal emphysema immediately beneath the leura

Figure 185 is a photomicrographic section taken from immediately elow the pleura You will note the thickened alveolar walls, the emphy-ema, and invading fibrous tissue.

Figure 186 is a higher power preparation It shows the nature of the ickening of the alveolar walls and reveals that these are lined with uboidal epithelium. One portion of the field shows these thickened walls eing invaded by fibrous tissue.

Figure 187 shows a massively fibrosed area with replacement of the alveolar tissue Scattered pigment particles and an area showing a collection of small round cells should be noted The patient died from terminal bronchial pneumonia The fibrous tissue is non-nodular



FIG 186 The thickened alveolar walls of the same case (fig 183)

Figure 188 is of a section of a lymph gland You will note the almost complete absence of fibrous tissue, but the massive collection of pigment particles

I mentioned that autopsy material from 2 persons who died from this disease had been submitted to Dr Gardner Shortly after he received and examined these he began animal experiments using stack fume and other material obtained from one of the plants engaged in the process Since his death it has been disclosed that one of the animals he inoculated

with fume developed a fibrous lung condition showing characteristics not unlike those exhibited by the human cases. It is likely that reports covering these observations will be forthcoming from the Trudeau Foundation in due course.



FIG 187 Fibrosis of the pulmonary parenchyma of the same case (fig 183) about deposits of inhaled dust

It may be surprising that cases of this disease should have been discovered only so recently when the process concerned had been in operation for a period of at least twenty years It is strongly suggested that cases may have occurred previously and were missed. Some years ago a partial survey covering certain of those in exposure was conducted in connection with the employees in one of these plants. The films prepared at that time were taken with a portable apparatus and were of poor quality Most of these films had been destroyed before the condition came to light A remaining film on one of the fatal cases shows shadowing strongly suggestive of early disease. At the time of the survey, however,

the shadowing was ascribed to tuberculous infiltration. A review of certain death records indicates a rather high death rate from pneumonia and coronary thrombosis among workers at this process These are at least suggestive It is intimated, however, that during the period when

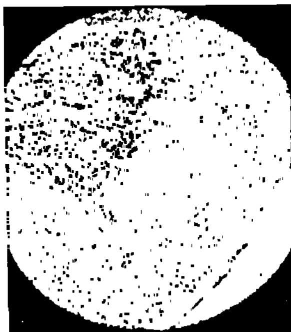


FIG 188 A tracheobronchial lymph node of the same case (fig 183) Although dust pigment has been deposited from the lung, nevertheless there is minimal reaction and no fibrosis

these cases occurred the process had been accelerated because of war needs During the war, production increased about ten times but there was not a corresponding increase in working staffs Thus the exposure in relation to the individual worker was considerably more intense than had previously been the case.

The etiology of the disease is still obscure There has been much speculation as to its cause, but nothing has been definitely established, except its relation to the furnace fume Experimental work is now being conducted in several places with a view to clarifying the situation It is hoped

that, in due course, these experiments will bear fruit and afford the answer.

In closing, I wish to draw particular attention to the radiologic appearances which constitute the earliest manifestations *of this disease. These* are often so slight that they may be missed entirely or, if they are noted, passed over as insignificant *These slight changes are important, however,* because certain cases advance very rapidly. When early changes are noted, *removal of the individual concerned from further exposure must* be seriously considered as this is the only method offering a reasonable *chance of effecting arrest of the process.*

Having in mind our experience with this disease it may be that the *situation in relation to some other exposures, at present considered harmless* but involving dusts or fume, should be reviewed unless, of course, *the workers in such exposures are now being checked at periodic intervals* by chest radiography. It is possible, as in this instance, that reliance on *the evidence of a single survey and on films of indifferent quality may* have influenced the opinion regarding the harmful nature of some of these exposures *This may be even more important if the opinion was* based on experience with the radiological manifestations of the effects of silica dust inhalation *for most of us are influenced by our previous* experience.

Discussion

C G SHAVER, M.D.*

Dr. Riddell's paper has presented many problems which are as yet unanswered It is very difficult to understand why an industry which has been operating for many years would suddenly bring to light the condition which he has described, with no apparent change in the physical properties of the materials used or in the manufacturing process. We have examined many patients from the abrasive plants situated in the Niagara Peninsula in years gone by and in view of the apparent individual susceptibility of some men to this disease it becomes *difficult to* realize why certain employees did not show well-developed disease pre-

* Superintendent, Niagara Peninsula Sanatorium Association, St Catharines, Ontario, Canada

vious to 1942. It is true that we have some X-ray material which suggests that the disease may have been present previous to the war years. The causes of death among men who worked in the industry are also suggestive but in no way conclusive that a few of them may have suffered from this particular malady.

It has been my privilege to do the clinical work on most of these patients and there are certain facts which stand out quite prominently. The rapidity with which certain individuals become incapacitated is striking, and in contrast to this we find a case who because of his age was retired from the plant after twenty-seven years continuous exposure to furnace fumes. He shows typical X-ray changes but has no disability. I believe, however, that any patient showing distortion of the diaphragm, and this is usually associated with some widening of the mediastinum, is in for serious trouble and again I am doubtful that even the best X-ray technic will always reveal the full extent of disease. This suggests to me that a more comprehensive survey of the group in relation to lung function is indicated.

Our chief problem, however, is the prevention of further disease among men who are exposed to the fumes, and because of the time which will likely be consumed in research investigation which is under way and which we hope will reveal the cause of the disease, it has become necessary to meet the situation without specific knowledge. Removal of the fumes needs no comment. Whether sufficient control in this manner will be completely effective, time alone will tell. In considering the medical aspects of control with present knowledge, certain facts stand out:

1. Adequate diagnostic films. We have had some experience using portable X-ray equipment and interpretation of some of these films has left much to be desired.

2. Pre-employment X-ray examination. This examination is necessary to eliminate the medically unfit. Since we do not know whether silica is a causative agent, it is imperative that tuberculous patients should not be employed, and furthermore, we have some evidence to suggest that acute pulmonary infections accelerate the condition so that rechecks following such episodes are indicated. It is felt that any patient with chronic lung disease should be eliminated from this particular type of work.

3. The immediate removal from furnace fume exposure of any man showing X-ray changes suggestive of the disease.



FIGS. 189-192

FIG. 189 Gross section of human lung The lesion is most apparent in
he deeper portions, and there appears to be a zone of more pronounced
action, about 1 cm beneath the pleura There is distinct emphysema of
e pulmonary tissue between this zone and the pleura FIG. 190. Gross
tion of lung This preparation, from a different area of the same lung
189), reveals similar changes FIG 191 Photomicrograph of lung
field represented appears air-containing in the gross section (figs
and 190), but a dense fibrosis of the alveolar walls with thickening is
rent here Approximately × 100. FIG. 192. Photomicrograph of
This field is located at the margin of the more dense subpleural zone
in fig. 189 Here fibrosis has become confluent, replacing all pul-
y structure Approximately × 100

4. Repeat X-ray examination of all men exposed to fumes at intervals of six months, or more often as indicated. It has been observed that those showing considerable X-ray change may progress materially over a period of six months, but it is not felt that an employee with a normal X-ray picture will show evidence of serious disease within a similar time limit, and I do not think that this latter group removed from exposure will progress to a degree which will cause incapacitation

Discussion

PHILIP C PRATT, M D.*

You have already learned how this problem came to our attention for experimental study so in the interest of brevity I will not go into the history of the work It may be well, however, to present a few illustrations of the nature of the lesions present in the lungs of one of the victims of this disease The gross sections of lung are particularly instructive (see figs. 189, 190, 191, and 192)

In our experimental studies we have used two specimens of dust obtained from one of the plants where these cases have been observed. The first sample had been collected on a furnace platform and passed through a 325-mesh screen. The second was a sample of "fume" collected from the air above a furnace.

Study of the sample from the furnace platform revealed it to be composed of particles ranging in size from 40 microns to the limit of visibility. By chemical analysis it contained a total of 6 8 per cent silicon dioxide. Free crystalline silica, however, determined by X-ray diffraction, composed only about 0 9 per cent The remaining 5 9 per cent of silica was, probably, in an amorphous form and may have been either free, or combined with bases as a glass It has not been possible for us to determine accurately the amount of this silica which is in a free form The major constituent of the dust was corundum, 50 per cent A variety of minor constituents, including ferric oxide, 9 per cent, and titanium oxide, 4 per cent, made up the remaining 43 per cent

This dust from the furnace platform was prepared for animal tests as a 5% suspension in saline solution and was injected intratracheally in

* Pathologist, The Saranac Laboratory, Saranac Lake, New York

guinea pigs in three doses of 0.5 cc. each, at weekly intervals. The animals were killed at intervals up to one year. The results of the experiment without going into great detail, reveal this dust to be essentially inert That is, the particles were phagocytized and produced no significant fibrosis within a year.

The other dust sample, "fume" from the stack of the furnace, was in fact a fume and consisted chiefly of particles beyond the resolving power of the microscope. Electron photomicrographs revealed particles ranging from one-half to a few hundredths of a micron in diameter. There were occasional particles larger than 1 micron Chemical analysis revealed a total of 32 3 per cent of silicon dioxide, and a total of 56 per cent aluminum oxide As with the platform dust, determination of the percentage of free silica was difficult By X-ray diffraction examination, no appreciable crystalline free silica or silicates could be demonstrated Therefore the silica was almost entirely in an amorphous form.

We feel that it is of great importance to know how much of the silica was free, and how much was combined with bases, in the form of glass As I have said, we have not as yet devised a reliable method for determining this point directly, however, we have certain information which leads us to believe that a considerable quantity of the silica was uncombined

This information can be presented under three headings First, there is a study carried out with the electron microscope. In this study the dust was mounted on a grid in routine fashion and photographed. The grid was then exposed to hydrofluoric acid vapor for some hours and was rephotographed Vacuoles of the size and shape of the original dust particles were found in the mounting medium Some of these vacuoles contained a slight residuum, interpreted as material originally combined with silica and left behind when the latter was volatilized by the hydrofluoric acid vapor Other vacuoles, however, were entirely empty, and the particles which they represented were presumably composed of pure, free silica We have thus qualitative evidence suggesting that at least some of the silica was free

Second, the X-ray diffraction pattern of the "fume" revealed lines corresponding to those of beta and gamma alumina. The lines of gamma alumina were strong, suggesting that a fairly large proportion of the

aluminum oxide present was crystalline, and, therefore, not combined with the silica.

Third, if the bulk of aluminum was uncombined, as assumed, and in view of the minor amount of other constituents of the fume, it appears that there was an insufficient quantity of metallic elements to combine with the silica to form silicates, so that a large proportion of the silica was probably free

This dust (the stack "fume") was injected intratracheally into guinea pigs in the same manner as the first, and the animals were followed by serial sacrificings at two, four, eight, and twelve months In the first two sacrifices, there was nothing of very great significance on gross examination Microscopically, there were compact clumps of dust cells with a slight fibrosis about the margins of the localized lesions. This was merely a capsule, and was considered to be of no significance At eight months, the gross appearance was much the same, although microscopically there did seem to be a definite, though slight, progression of the fibrosis, in the capsules of the lesions At twelve months, gross examination revealed fibrous adhesions on the pleural surfaces, and a long depressed linear pigmented scar running through an entire lobe Microscopically, there was found in that area a band of delicate, diffuse fibrous tissue, which, as Dr Riddell has said, closely resembles the fibrosis found in human cases

There was not a great deal of this fibrosis to be seen in the section because the section ran across the linear band of fibrosis This finding, however, combined with the gross observation of definite lesions, suggests that a pretty definite fibrosis had occurred

More comment should be made on this experiment, I think The lesion is remarkably similar to the ones seen in human cases, but since it apparently developed rather abruptly between eight and twelve months, we may be dealing with some artefact The experiment is now being repeated to see if these results can be reproduced

Further interest in this matter is aroused by the observation made by the electron-microscopist, who said that spectrographic analysis of the lung residue from autopsied cases gave a very similar pattern to that of the stack fume itself Thus from all points of view, the stack fume is incriminated as the agent causing this disease

It is interesting to speculate concerning the relationship of the physical

form of this dust to the lesion producer. We have done experiments with vitreous silica, an amorphous form we knew to be in the free state and to be practically pure silica. This material produced ordinary, typical silicotic nodules. Thus, it appears that, if silica is at work in this disease, its effect is greatly modified by the presence of other components of the dust. The steps required to resolve this problem seem to involve experiments with pure preparations of vitreous silica and gamma alumina, both alone and in known mixtures.

CHAPTER 31

Chemical Aspects of Shaver's Disease

C M JEPHCOTT, PH D.*

The specific lung changes which were described by Dr Riddell occurred only among those workmen who were exposed to the fume given off by the electric furnaces in the manufacture of an alumina abrasive from bauxite and they did not occur among the workmen who were not so exposed.

The method of producing this artificial abrasive was discovered and patented by Jacobs in 1900 and a few years later the product was made commercially on a small scale in the United States. It was not until 1914 that the first plant to produce this abrasive in Canada was built in the Niagara Peninsula in Ontario Later three similar plants were constructed in the same district

The production of this alumina abrasive increased from 20,000 tons in 1933 to 86 000 tons in 1937. Due to the war demand, the output reached a peak in 1943 of 190,000 tons At present, the rated capacity of the Canadian plants is approximately 200,000 tons per annum

Calcined bauxite is the chief raw material used in the process To this is added a small amount of coke to reduce some of the oxides and also some iron or steel which acts as a purge to remove some of the undesirable impurities in the ore

Very little change occurred in the composition of either the coke or the iron used during the past few years and any variations which were noted were not considered significant The four companies obtained their bauxite from a large deposit situated in the state of Arkansas. Representative samples of the bauxite were collected from three of the plants and analysed chemically and spectrographically. The spectrographic analyses

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showed the presence of some twenty-five different elements. The chemical analyses shown in table LXXV indicate that between 1939 and 1945 only small variations occurred in the composition of the bauxite ore used. At present, the industry is turning to South America for its source of supply. The South American bauxite contains a higher percentage of alumina with a corresponding lower percentage of some of the major impurities.

TABLE LXXV CHEMICAL ANALYSES OF CALCINED ARKANSAS BAUXITES

	Plant A *1939* (per cent)	*Plant A* *1944* (per cent)	*Plant B* *1939* (per cent)	*Plant B* *1945* (per cent)	*Plant C* *1942* (per cent)	*Plant C* *1945* (per cent)
Loss on ignition (<120°C)	0.59	0.20	0.15	0.83	0.38	1.35
Loss on ignition (>120°C)	0.42	0.57	1.17	0.61	1.87	1.82
SiO_2	4.48	5.32	4.84	7.22	7.16	5.55
Al_2O_3	80.73	81.75	85.17	77.46	79.19	79.66
TiO_2	3.20	3.28	3.65	4.05	3.47	4.10
Fe_2O_3	8.73	7.35	3.51	8.94	6.55	6.43
ZrO_2	0.51	0.68	0.39	0.30	0.31	0.32
MnO	0.35	0.32	0.28	0.13	0.29	0.11
CaO	0.27	0.15	0.15	0.17	0.23	0.23
MgO	0.23	0.10	0.08	0.00	0.01	0.00
Na_2O+K_2O	0.38	0.04	0.45	0.08	0.37	0.05
P_2O_5	0.11	0.24	0.16	0.21	0.17	0.38
Total	100.00	100.00	100.00	100.00	100.00	100.00

The type of electric furnace used for the manufacture of this alumina abrasive has a capacity of about ten tons of mix. The furnace is charged initially with about a third of this amount and the remainder is shovelled in periodically when necessary. The length of time taken to make a run—from the time the furnace is charged initially to the end of the fusion time—is about one day. During this time the temperature of the mix reaches about 2000° C.

... employed in

furnaces during the heating cycle. The furnace buildings were designed to provide natural ventilation by ... much use as possible of the temperature ... due to th... furnaces. In some cases, stacks have ... over the ... to direct the fume towards

the opening in the roof. In a few instances, the efficiency of these stacks has been increased by the installation of fans

Air samples were taken close to the electric furnaces and on the adjacent working platforms by means of a Bausch and Lomb dust counter, a Greenburg Smith impinger, an electrostatic precipitator, and a vacuum cleaner.

TABLE LXXVI CHEMICAL ANALYSES OF ELECTRIC FURNACE FUMES

	Plant A *1937* (per cent)	*Plant A* *1945* (per cent)	*Plant B* *1946* (per cent)	*Plant C* *1946* (per cent)	*Plant D* *1946* (per cent)
Loss on ignition (<110°C)	0 68	0 41	0 35	0 47	0 65
Loss on ignition (>110°C)	3 23	2 45	2 96	2 15	3 93
SiO_2	44 24	32 32	30 11	28 93	44 00
Al_2O_3	41 60	56 43	52 34	62 15	40 69
TiO_2	0 98	0 60	0 57	0 25	0 35
Fe_2O_3	3 68	3 83	4 40	2 50	3 03
ZrO_2	0 17	0 20	0 07	0 08	0 09
MnO	2 79	1 59	1 50	1 07	2 78
CaO	0 00	0 06	0 15	0 15	0 10
MgO	0 58	0 39	0 33	0 56	0 86
Na_2O	0 45	0 50	2 26	0 84	1 12
K_2O	0 95	0 86	1 37	0 88	2 13
P_2O_5	0 35	0 31	0 22	0 22	0 38
Total	99 70	99 95	96 63	100 25	100 11

The samples of fume collected at the four plants by means of the vacuum cleaner were used to make a chemical, spectrographic, and X-ray diffraction analysis The determination of the particle size was made by means of an election microscope using 24,000 magnification The fume consists chiefly of amorphous material with the particles spherical in shape and ranging in size from somewhat under one micron down to a few hundredths of a micron The spectrographic analyses showed the presence of some twenty-five elements and the results of the chemical analyses are reported in table LXXVI.

Dust counts were made on samples collected by the Bausch and Lomb dust counter and by the Greenburg Smith impinger The average counts in the four plants ranged from 11 to 300 million particles per cubic foot of air These differences are rather surprising but it must be realized they were done at various times of the year and under different weather con-

ditions. Furthermore, it must be pointed out that the particle size of the fume was such that relatively few of the particles present could be seen under a microscope.

The samples of dust collected by means of the Greenburg Smith impinger and the electrostatic precipitator were weighed. The average weight of these dust samples collected in the four plants ranged from

TABLE LXXVII. CHEMICAL ANALYSES OF LUNG ASH

	Case 8 *J.F.* (per cent)	*Case 11* *H B* (per cent)	*Case 17* *R L* (per cent)
Loss on ignition (<110°C)	0 30	0 43	0 07
Loss on ignition (>110°C.)	1.55	3 88	1 18
SiO_2	24 80	30 48	21 18
Al_2O_3	40 50	30 36	28 86
TiO_2	2 88	2 50	1 25
Fe_2O_3	5 10	4 00	5 92
ZrO_2	0 25	0 24	0 15
MnO	0 60	0 50	2 25
CaO	1 44	2 50	3 80
MgO	0 69	0 70	0 24
Na_2O	3 82	4 98	5 14
P_2O_5	13 91	12 50	26 09
K_2O	3 69	5 51	3 76
SO_3	0 58	0 81	0 32
Cl	0.10	0.76	0 06
Total	100 20	100 13	100 27
Less O for Cl	0 02	0.17	0 01
Total	100 18	99 96	100 26

about 10 to 40 mg. per cubic meter of air for the samples taken with the impinger and from about 12 to 100 mg. per cubic meter for samples taken with the precipitator.

Lung tissue was obtained at autopsy from workmen who had been exposed to the fume for periods of three to five years. For spectrographic, chemical, and X-ray diffraction analysis, the lung ash was obtained by heating the lung tissue at moderate temperature. The results of the spectrographic analyses were very similar to those given by the furnace fumes and, as would be expected, all elements present in the fume were present also in the lung ash. The X-ray diffraction analyses were comparable to those of the furnace fumes in so far as they both showed

considerable amorphous material as well as the presence of alpha and gamma alumina.

The results of the chemical analyses are shown in table LXXVII. It is evident that the samples of lung ash are characterized by their high percentage of alumina and silica as well as by the presence of other constituents in amounts not usually occurring in the lung tissue.

It was thought that the inhalation of alumina and silica might be accompanied by an excess excretion of these two constituents. Spot samples of urine were collected from exposed workmen and from members of our laboratory staff. The excretion of aluminum was found to vary within wide limits even in the unexposed individuals and there seemed to be no significant difference, on the average, in the amounts found in the urine of the exposed and unexposed groups. The urinary excretion of silica varied also within wide limits but, on the average, the excretion of silica in the exposed group was greater than in the unexposed group This difference might be caused by some other factor than the inhalation of silica

Experiments on the solubility of the fume are in progress but are not sufficiently complete to report at this time.

Discussion

GORDON R FINLAY, PH D *

Supplementary to what Dr. Jephcott has told you, I should like to add a few details of the process. The furnaces (fig. 193) employed for fusing bauxite amount to steel pots which are water cooled on the outside. These furnaces are thermally self-insulated, that is, insulated by a layer of unfused bauxite, except that they do have a refractory bottom. In consequence of this insulation, the molten bath is always in contact with unfused material and this fixes the operating temperature of the furnace in the same manner as the temperature of an ice and water bath is fixed

The furnace operates as a combination of arc and resistance. The electrodes are made of carbon and dip into the bath to form a completed circuit which consists of an arc from the electrode to the bath, a current

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through the bath itself and an arc from the bath to the electrode again Usually, there are two electrodes to a furnace but some are operated on three-phase current using three electrodes. In operation the arcs are usually covered by unfused mixture.

The furnaces are fed with bauxite ore (low silica grade) which is calcined and crushed to ¼-inch and finer. With the bauxite ore it is cus-

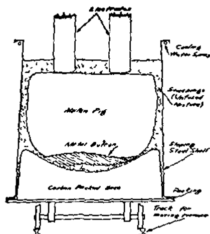


Fig. 193 Schematic drawing of furnace for fusing bauxite.



Fig. 194. Electron photomicrograph of fumes from furnace fusing bauxite.

tomary to mix iron turnings and metallurgical coke screenings. The coke acts as a reducing agent which lowers the silica, iron, and titania contents of the ore by reducing the various oxides to the metallic state. The iron turnings are added as a purge so that the net effect is a sort of upside down metallurgy in which the slag is recovered as the product, while the metal phase is the by-product

The mixture is fed to the furnaces by a man using a shovel. Naturally, he comes in fairly close contact with the fumes produced by the furnace. Also exposed to these fumes are the crane operators who work in a craneway above the furnace level or close to it and in some cases the men who tend the storage bins which contain the mix

Dr. Jephcott has already described for you the nature of the fumes but I should like to emphasize again some of the unusual features of this exposure. Actually, the workmen encounter both dust and fumes, the

dust consisting largely of the fines from the bauxite and other constituents of the mixture and being almost entirely coarser than five microns. The fumes are produced from the furnace and are almost entirely finer than one micron in size. Numerous variations in exposure have been observed. These vary with the weather conditions and the ventilation conditions, as well as with the scale of operations. The temperature, the humidity,

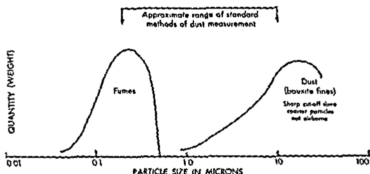


FIG. 195 Particle size of dust and fume in the neighborhood of furnaces fusing bauxite.

the season, the wind direction rain, the operation of the fans, stray currents, and many other factors influence the concentration of the fumes

It should be stressed again that there is no satisfactory method for measuring this exposure, nor are there any standards for interpreting such figures as may be obtained As shown by the electron photomicrographs (fig 194), it is certain that a large and probably variable proportion of the fumes lies in the size range which cannot be counted by any of the standard methods We have, nevertheless, made some attempts to measure the fume concentration (fig 195), using the Owens Jet apparatus and counting the deposit obtained at a magnification of 500. By this means we have obtained counts showing fume concentrations ranging from 20 million to 1200 million particles per cubic foot of air Occasional samples which were too dense to count must have exceeded the upper level cited It should be pointed out, however, that even these high values do not indicate a high *weight* concentration of material. I believe that Dr Jephcott's figures as taken with the M.S.A electrostatic precipitator represent the most accurate values for the weight concentration of the fumes

As shown in the electron photomicrograph, the fume particles are spherical in form and range downward in size from one micron. For the medical people, I should like to stress that these particles are smaller than bacteria and will not show up in tissue sections studied by ordinary technics.

All studies to date have indicated that these fumes are truly amorphous The chemical constitution indicates that they contain both alumina and silica as major constituents which would seem to show that we are dealing here with a glasslike alumina-silica mixture. There is some evidence that the silica may be concentrated in the fines or that at least the fines are richer in silica. If this is the case, it would explain Dr. Jephcott's results on the samples collected by the electrostatic precipitator. This instrument is believed to be more efficient than the impinger in collecting the fine particles. In at least two plants the samples collected in the electrostatic precipitator were much higher in silica than the samples collected at the same times and places, respectively, with the impinger.

The amorphous alumina or alumina-silica glass which is found in these fumes has not previously been encountered elsewhere. The burning of aluminum metal in air or oxygen gives a product which is identifiable as gamma alumina.

Three possible modes of origin of the fumes may be considered, as follows:

1. They may be produced by direct volatilization of the mix at the temperature of the arc, that is, in the neighborhood of 4000° C This is the most likely source.

2. They may arise from the vapor of the bath itself which is at approximately 2000° C. It would be expected that silica would have an appreciable vapor pressure over this bath but very little alumina would be evolved by such a mechanism

3. By reduction of the oxides to the metals (the carbon present acting as a reducing agent) and subsequent reoxidation of the metal vapors.

None of these three possible mechanisms for the production of fumes fits too well with the observed facts Similar fumes are encountered in the operation of silicon and ferro-silicon furnaces and also in the practice of arc welding.

A sample of lung ash taken from one of these cases showed the same analysis as did the fumes, if the sodium, potassium and phosphates nor-

mally present in lung ash were subtracted A sample of lung tissue was ashed with 30% hydrogen peroxide An electron photomicrograph taken through the courtesy of the Aluminum Company showed that this lung ash contained the same sort of spheres showing the same properties as those originally present in the furnace fume This we consider to be proof that particles of the fume as fine as 0 02 microns in size were actually deposited in the lung

I should like at this time to pay a tribute to the medical people for their discovery of this disease. Dr. Shaver and Dr. A. G. Strang encountered it independently Each of them, on the basis of a single case, was prepared to say that this disease was something new and different. It is perhaps fortunate that the industry was concentrated in such a small area that they were able to compare notes Otherwise, the significance of this exposure might readily have been overlooked.

I have been struck in reviewing the data on these cases with the fact that practically nothing is known about the metabolism of either silica or alumina

Summary

THEODORE F. HATCH*

We may summarize the present discussion of the etiology of Shaver's disease in a few broad statements

1 The disease is clearly of occupational origin, as evidenced by the high incidence in a relatively small group of workers within the synthetic abrasive industry who are exposed to the fumes from the electric furnaces used in the production of fused alumina. The specific influence of the fume is indicated by the apparent absence of the disease among other workers in the industry, who have some dust exposure from the original batch materials and from the crushing of the fused product, but little, if any, fume exposure

2 The fume is rich in alumina and silica, both apparently in the free state The percentage of silica in the fume is six to ten times higher than in the unfired batch, with a correspondingly lower percentage of alumina

3 The fume is characterized by its small particle size—generally smaller than 0 5 micron and extending down to about 0 02 micron

4 The specific causative agent within the fume has not been identified.

5 Compared with silicosis, Shaver's disease may develop in a remarkably short time, resulting in profound pulmonary damage and even death in as many months as it takes years to produce advanced silicosis.

6 The sudden appearance of the disease in high incidence during the war has not been fully explained. No significant change in process or method of operation was discovered as a common factor in all of the plants in the industry. Presumably, the disease resulted from the increase in fume concentration accompanying higher production It is of interest, however, that the fume concentration during the war period was not spectacularly higher than the prewar level, judging from limited data

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It is evident that systematic research is needed to provide an adequate explanation of the etiology of Shaver's disease. In the meantime, however, the industry is taking active steps to collect the fumes and so remove the causative agent from the industry. Although there are certain mechanical difficulties, ventilation is expected to reduce the fume concentration well

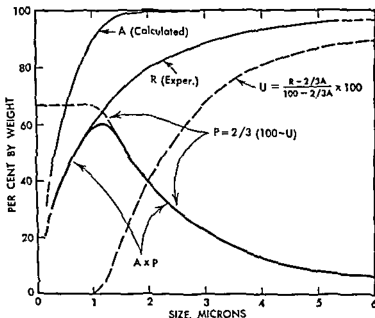


Fig 196 Retention of inhaled dust particles relation between percentage retained and particle size

below the prewar level This action recognizes the immediate practical problem but does not reduce the need for continued research until the etiology of the disease is fully explained

Interest in Shaver's disease extends far beyond the synthetic abrasive industry since certain implications which must be drawn from this experience are at variance with present views in respect to the action of particulate matter in the respiratory system

Of outstanding significance is the extremely fine size of the fume particles (0 02 to 0.5 microns) Heretofore, particles of this size have been commonly regarded as having little significance in the development of pulmonary fibrosis, the argument being that such particles are not re-

tained in the lungs to any significant extent. Retention of fine particles in the over-all respiratory system is, indeed, low compared with the retention of relatively coarse particles, as shown by the accompanying curve (fig 196) from Van Wijk and Patterson.[628] This curve, however, does not distinguish between alveolar deposition and retention in the upper respiratory tract, the latter being of no interest in respect to the development of fibrosis. Furthermore, it can be said at once that the high percentage retention exhibited by the larger particles necessarily means that many of them are deposited in the upper portion of the respiratory system. This follows from the fact that alveolar retention can never exceed the percentage of inhaled air which penetrates to the lung depths (approximately two-thirds) Based upon this reasoning, we have calculated elsewhere[272] that alveolar retention of 5 micron particles is less than 5 per cent, compared with the 95 per cent over-all retention shown by the Van Wijk-Patterson curve. Continuing the calculations to smaller particles, a curve was constructed for alveolar retention in relation to size. This is also shown in the figure. Although based upon over-simplified calculations, this curve suggests that alveolar retention of particles below 0 5-micron size is as great as for larger particles, thus opposing the earlier reasoning in respect to the significant role of fine particles. The Van Wijk-Patterson curve does not extend below 0 25 micron because of limitations in microscopy. It can be successfullly argued, however, that for smaller particles, alveolar retention will reach a minimum and then increase again because of the increasing influence of Brownian motion, ultimately approaching the retention of a soluble vapor (approximately 66 per cent) Thus, in the present case, with an average particle size in the fume of about 0.1 micron, the amount deposited in the alveoli may very well be higher than the minimum indicated by the curve.

The rapidity with which Shaver's disease develops is another feature of outstanding interest. Exposures are expressed in months rather than in years, as in silicosis. Again, the fineness of the particles is undoubtedly the influencing factor, in accordance with laboratory studies which have shown that the rapidity with which fibrosis develops increases with decreasing size. In Shaver's disease one sees generalized pulmonary fibrosis without the silicotic nodules which are regarded as the essential and unique pathologic feature of silicosis. Does it necessarily follow, as a consequence, that silica is not the damaging agent? Is it not possible, on

the contrary, that we are seeing here a different manifestation of damage by silica, resulting from its unusually fine size and consequent rapidity of action? Present thinking in respect to silicosis comes largely from and is, perhaps, limited by the experience with the disease in a few specific dusty trades—hard rock mining, granite cutting, and the like—in which the dust contains an overwhelming amount of relatively coarse particles Should silica prove to be the causative agent in Shaver's disease some significant revisions in our views would necessarily follow. It would, for example, involve new methods of analysis.

Dr. Jephcott has pointed out that the standard methods of dust sampling and analysis are of little value when dealing with submicroscopic particles The electron microscope has to be substituted for the optical microscope Concentrations must be reported in terms of weight instead of count. Variation in composition with particle size, degree of flocculation of the fume, and other physical and chemical characteristics need careful study. The X-ray diffraction apparatus and spectroscope become essential tools. New methods of sampling are required in order to apply these analytical techniques usefully.

Discussion

DR A R SMITH I would like some speculation, preferably from Dr. Riddell, as to why, in the event this disease may be due to silica fume, the presence of the alumina fume may not act as a protective device as it does where the two dusts are present?

DR RIDDELL I cannot answer that Perhaps Dr Dudley Irwin might be able to do so

DR IRWIN In order to render silica insoluble by means of alumina, it is necessary to have a source of alumina that readily takes on water and becomes adsorbed to the surfaces of the silica particles. This type of alumina is not the type that takes on water and becomes adsorbed to the surface of silica particles

MR URBAN Is there any relation between the temperature of the furnace and the free silica concentration in the furnace fume? Would the percentage of free silica in the fume be increased if the furnace temperature were raised?

DR. IRWIN: The temperature of the furnace is fixed within reasonable limits, like melting ice in water which remains close to zero. In the furnace molten bauxite is in contact with solid bauxite, so the temperature of the mix is reasonably constant. If the temperature of the furnace were raised, a higher percentage of the siliceous material would probably volatilize in the form of silica fume

DR VORWALD: The Saranac Laboratory is engaged with researches concerning the pulmonary damage resulting from the inhalation of very fine particles of a variety of dusts. The particles range from 1 to 0 002 micron in size. At the present time, it appears that dusts containing particles of free silica less than 1 micron in size are capable of producing a diffuse pulmonary fibrosis characterized by marked thickening of the alveolar walls and distortion of the alveolar spaces usually emphysematous in type It is evident that particles of free silica, even in the ultramicroscopic range, are retained in the lung and produce profound pulmonary damage The lower limits of that range have not been established. In this respect it is pertinent to inquire whether all active dusts inhaled from the atmosphere will be retained in the lung and produce damage of greater intensity as the particle size decreases What role the temperature, humidity, and recent fracturing of the dust, and also its piezoelectric property, might play in such damage is also debatable.

MR HATCH There is still a great deal to be learned about the retention of particles in the immediate zone of 0 25 micron. For still smaller particles, of the order of hundredths of a micron, retention may actually increase because of Brownian motion, and thus approach the behavior of a highly soluble vapor which is retained to the maximum extent permitted by the ratio of alveolar to total tidal air.

DR BRODKIN: Have you been able to prevent these pneumothoraces from recurring?

DR SHAVER. We haven't been able to do a thing with the pneumothoraces In those cases having a marked fibrosis of the lungs, we were not able to obtain any re-expansion of the lung by frequent withdrawal of air.

DR. FINLAY I would like to add to what Mr Hatch has said We do have evidence that particles smaller than a quarter of a micron are retained in the lung. One of the samples of lung ash sent to Saranac was subsequently examined by electron microscopy and these small

round particles were found there, apparently unchanged in the lung ash They were still in the same shape and were below a quarter of a micron in size.

DR. IRWIN. I might mention an exposure to this type of bauxite before it reaches the abrasive plants The mining and crushing of this bauxite is attended with practically no dust exposure due to the presence of inherent moisture After the bauxite is crushed, it is put through a drying kiln and subsequently loaded in railroad cars. This operation produces considerable dust

When I first saw this exposure, I was apprehensive about the men who worked on this job These men were examined clinically and films of the chest were made No evidence of lung pathology was found attributable to this dust exposure One worker, so examined, had been exposed for twenty-three years.

DR SHAVER. That concurs with our studies on the men that unload the cars.

DR VANORDSTRAND: Has there been anything significant regarding diaphragm activity?

DR SHAVER The diaphragm activity is very limited

DR VOSBURGH Is there any chance of feeding those furnaces mechanically, and is there any chance that those round droplets shown by the electron microscope are simply a mixture of different sized aerosols?

DR FINLAY It is quite possible that the furnaces can be fed mechanically, and I think the industry is approaching that

However, the present capital investment is tied up in hand-feeding, and it may be some little time before that can be changed over. Also, whenever you change one of these arc processes over to a mechanical process, you will run into trouble I suspect it will take some time to run out the "bugs"

And the other question was what?

DR VOSBURGH As to the possibility of those round droplets shown by the electron microscope being simply a mixture of different sized aerosols.

DR JEPHCOTT. I think that the small spherical particles, as shown in the electron microscope photograph, consist chiefly of a mixture of very fine amorphous alumina and silica particles of varying size

PART SEVEN

Compensation for Occupational Disease

CHAPTER 33

Introduction

THEODORE C WATERS*

On your behalf and my own, I would like to express to Doctor Vorwald, Doctor Packard, and Mr Bowditch, together with other officials of the staff of the Saranac Laboratory, our thanks for the privilege of participating in this meeting The Saranac Laboratory occupies a unique position in the field of industrial hygiene I think it is fair to say that the activities and work of the Laboratory as conducted by Dr Gardner, Dr Vorwald, and their associates, have enjoyed the full confidence, respect, and cooperation of all persons interested in or concerned with health problems in industry During the past when many of us have been perplexed with some new problem in the field of occupational diseases, our eyes have turned to the Laboratory and we have sought their counsel and advice That counsel has been of the best that was obtainable . . . thoroughly professional in its nature, scrupulously honest in its opinion, given in the hope that working conditions may be improved for the protection and welfare of those subjected to the hazards of industrial exposures

Today we meet to discuss current viewpoints in matters of compensation, with particular reference to pulmonary and other occupational diseases Mr Bowditch is to be congratulated upon the program that he has prepared I happen to know something about his efforts in the completion of that program, and it has indeed been a real task We are most fortunate in having present representative speakers to discuss the various viewpoints involved in workmen's compensation I feel certain that all of us will not be in agreement, that views will be expressed to which we cannot subscribe, but I know that each of us desires those with whom we may disagree to have the opportunity to express their views and that

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none of us will have any hesitancy in expressing our own criticism of those views.

Our commissioners administering the workmen's compensation laws in the different states are confronted with many problems. The role of these administrators is not an easy one. The basic purpose of the compensation acts is to award compensation for those who suffer disabling injuries arising out of and in the course of employment. In the field of occupational diseases many perplexing questions arise in the administration of these laws, and many of these problems will be discussed here today. Suffice it to say that we have not found the answer to all of the questions presented in the framing of occupational disease legislation, nor have we found all the answers in connection with the administration of these laws. I hope and expect that the current session will make a valuable contribution to our knowledge and experience in this field.

During the sessions of our respective state legislatures countless bills proposing to amend or re-enact provisions of the workmen's compensation laws are dropped into the hopper of the various state assemblies. It is probably fair to say that throughout the country and in the federal congress thousands of such bills are introduced. We must bear in mind that the compensation acts themselves are of relatively recent enactment. All of the states except Mississippi now have workmen's compensation acts, and under the laws of thirty-nine states,* the District of Columbia, and the Territories of Hawaii and Puerto Rico, as of May 1947, occupational diseases were compensable. In the remaining states where no provision is made for occupational disease compensation, the injured employee may or may not have the right of common law action against his employer for such injuries. We find that in the large industrial states the matter of occupational disease compensation has received careful attention, that the original laws have been amended and improved in the light of experience of administration. None of these laws is perfect nor is their administration perfect, but they have and should serve the purpose for which they were designed, that is, to provide reasonable compensation for victims of potential industrial hazards that produce

* [illegible] Delaware, Florida, Georgia, [illegible] higan, [illegible] lexico, [illegible] Island, [illegible] s, and [illegible] Wisconsin

disability or death. Prior to the enactment of these statutes, the injured employee was limited to a right to common law action against his employer, based upon negligence, and in that proceeding employers could raise the common law defenses of: (1) assumption of risk, (2) plaintiff's contributory negligence, or (3) negligence of the plaintiff's fellow servants.

In common law actions issues were tried before juries, and procedure was subject to the intricate technicalities and delays under that system. Society came to recognize the social need for some system of law that would impose upon the employer the obligation of insuring the health and safety of his employees, granting to the employee compensation for injuries sustained and wages lost irrespective of the fact of negligence of the employer By the compensation acts the legal liability of the employer has changed from that imposed by common law to that of an insurer, and the compensation acts prescribe schedules of compensation for the various types of injuries, with a limitation of monetary liability upon the employer for his obligations Generally speaking, the laws so enacted have been administered satisfactorily As evidence of that fact, I know of no intelligent effort in any of the states to effect repeal of the compensation acts They are part and parcel of social legislation, essential for the conduct of our industrial activities, and while some of the laws may have defects, I believe that their administration has proven beneficial, not only to the employees, but also to employers

The Industrial Medical Practitioner's Point of View

LEMUEL C. McGEE, M.D.*

A symposium on workmen's compensation for occupational disease risks a variety and disparity of observations equal to the descriptions of an elephant given by three blind men in an ancient fable. What I shall have to say on this subject is unquestionably conditioned by my own particular experience. This is the view not of *the* physician in industry but the view of *a* physician in industry. I shall make no distinction between pulmonary and other occupational disease.

It is not easy to define "occupational disease" clearly and satisfactorily The term "occupational disease" is useful, however, for its etiologic connotations of pathologic or physiologic changes in the body of a worker due primarily to circumstances of occupation A term does not lose its usefulness merely because of difficulties in definition. The physician diagnosing so common a disease as pneumonia repeatedly faces situations where he has difficulty in saying where hyperemia, atelectasis, pneumonitis, and other morbid states of the lung end and pneumonia begins Yet for purposes of diagnosis and treatment "pneumonia" is a useful term. Similarly, I consider "occupational disease" an adequate concept.

Occupational disease receives compensation consideration in our various states at present through one of four categories.

1 Broad coverage for all occupational diseases
2 Coverage for a specific list of occupational diseases
3 Coverage of some occupational diseases through a liberal, and possibly prostituted, definition of the term "injury" as it appears in the statutes dealing with industrial accidents
4 No consideration at all

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It is my opinion that an all-inclusive consideration of occupational disease for compensation is the proper goal Actually, we have seen in the past few years a tendency for the various states to move upward from category 4 to category 3, and so on in the above list. Why have *many men who are experienced in the administration* of our existing compensation laws opposed the adoption of the theoretically desirable broad coverage law for occupational disease? I think they fear an extension of serious difficulties, yes, even improprieties, in the administration of existing compensation laws, and they fear that broad coverage laws will be interpreted to offer a limitless system of compensation against all ailments of mankind and infirmities of old age at industry's expense. If the latter situation ensues, the statutes will fail in their purpose of *promoting the investigation, the recognition, and the prevention of true* occupational disease In this matter we touch the broader field of the economic and physical welfare of a society of men who have, after all, a limited span of life Should not workmen's compensation as such limit itself to injury and disease arising from and because of the workman's occupation, and leave to the broader consideration of the nation's health such matters as insurance for sickness and the better application to all the nation's citizens of preventive and therapeutic attributes of medical knowledge?

The pertinent issue to the physician *is not what the compensation statute promises but what the administrative system for the statute actually delivers* It is my observation that in general both industrial management and insurance carriers readily accept their responsibility in the clear-cut compensation claim It is in uncertain situations or in instances of bad faith on the part of one or both parties that the state compensation commissioner must intervene Those who stand to profit, under the contingent *fee arrangement, aggravate his difficulties by persuading workers to over*-estimate the value of their legal right to court controversy in compensation cases In addition, physicians who testify are to blame repeatedly for a confused commissioner and an irrational decision. The administrative officer is confronted too often by conflicting and prejudiced testimony enthusiastically presented by physicians retained by opposing sides The latter defect has been examined repeatedly and has led to many proposals aimed at its correction The better known of these suggestions are. (1) the appointment of a medical arbiter for each state or board,

(2) the creation of a board of physicians to deliver a purely medical report to guide the commission, (3) the formation of a state occupational disease institute to investigate all occupational diseases and to make facts available whenever wanted, and (4) a board of censors composed of physicians whose function it is to investigate instances of perjury or grossly illogical and untenable medical testimony and report its findings to state examining boards for action under the latter's medical licensing power.

I am in sympathy with the aims and see merit in some of those proposals. I am not sure, however, they will accomplish what they are set forth to do. They imply some degree of supererogation of the responsibilities resting in a compensation commission and tend to make a judge of the physician Will such suggested superstructures on the compensation commission do more than divide authority, weaken responsibility, transfer an administrative headache to a new agency and result in further delaying decisions? Do not such suggestions smack at least of an undemocratic, if not an illegal, procedure by limiting a claimant's rebuttal rights on questions of fact? I am not of the opinion that I and other members of my profession have the impeccability necessary to prevent some arbitrary and perhaps wholly illogical decisions even under the more promising of the proposals whereby medical decisions are placed by edict entirely in medical hands. In my experience commissioners now are glad enough to leave medical matters in the physicians' hands. The commissioners do groan and become confused by the variety of authoritative medical opinions thrown back at them here and there. Would enough be gained to justify the methods suggested—methods which are designed to separate the medical wheat from the chaff—methods which, it is hoped, would get facts on disease and injury, their cause and extent, clearly before the commission?

It is my view that far too many compensation decisions have been incorrect on the basis of fact when occupational disease was made part of the question. We should strive to increase the public confidence in the administration of existing systems of compensation by better performance Then broad coverage of truly occupational disease will be more acceptable to all parties involved

Why am I concerned with these decisions which to the physician are illogical and unjust? Am I troubled for the sake of industry? Not at all.

Such items are inconsequential in the total cost of production and, whatever the cost, it is of necessity ultimately absorbed by the consumer of the industrial product. Am I concerned for the sake of the insurance carrier offering compensation coverage? By no means. The premium rate is adjusted at suitable intervals on the basis of experience by the insurance company.

I am concerned by the wrong done to the claimant who receives an unjustified award and by the wrong done to his fellow workers The physician in industry finds that irreparable harm can and has been done to the man who at first glance seems merely to have received a windfall through an improper award The harm may develop in several ways The affirmation of a disability which does not exist may lead to a "whipped dog" attitude if not to a *frank neurosis in the man* *One may* thereby stimulate his lust to get something for nothing Should he know that his claim was not bona fide in that his disease was not occupational in origin, he sees in the award confirmation of the pernicious doctrine, now too prevalent in our generation, that a shrewd man can get along without earning his way, that acquiring a good "racket" here and there is the chief aim in modern life. Such a man is less a man, less a citizen, and in turn more of a liability in a democratic society The man's fellow workers are not fooled. Some look the facts over and conclude that they too may as well fabricate a claim to obtain some of the financial "gravy" that is being handed out. The fundamentally honest worker looks at the award and asks himself if genuine effort to be worthy of his hire is worthwhile. The unjust compensation decision gives him good reason to question the necessity for honesty in human affairs The morale of the industrial organization gets a body blow

The physician in industry lives with these results and knows them well The physician sees his fellowmen more intimately than do many others We should like our fellow citizens to remember one stubborn fact That is, the finest and most ideal plans for social and economic betterment not only will fall short of their aims but may bring on disaster if these plans are not wisely administered under a wholesome consideration for the true nature of man, for his weaknesses as well as his virtues

Can the ends of justice be served without radical changes in the administrative setup? I think they can How can this be done? To begin with, the education and training of the physician must better acquaint

him with his role in supplying testimony in compensation claims The medical schools are gradually increasing their attention to the teaching of industrial medicine Some of us would like to see this emphasis in medical education pushed with greater vigor. Even so, progress is being made Physicians should be expected to reach and justify one of three conclusions on the subject of the relationship of a given illness to occupation. The possible conclusions are: (1) that the illness beyond reasonable doubt resulted from occupation, (2) that the illness beyond reasonable doubt did not result from occupation; or (3) that one has not sufficient knowledge to justify an opinion on the cause of the disease. Sometimes sufficient knowledge does not exist to justify a medical decision on the influence of occupation, if any, in an illness The cases in the latter category should be recognized as such but I shall not comment here on their disposition I am concerned rather with the case where sufficient *knowledge on the cause of disease is available to mark it clearly as non-*occupational in origin yet wherein an award is given to the claimant.

It seems to me that compensation commissioners cannot avoid the *responsibility of testing the probity of testimony which they receive* Were I to set out to find a man who believes that the earth is flat I am sure I could find him My securing him for testimony does not mean that a *commissioner should decide the nature of the earth's surface* on such evidence I know of no scheme which will wholly prevent the introduction of incorrect testimony. The commissioner must exercise judicial dis*cretion in evaluating evidence—there is no other way.* If his own knowledge is not sufficient, there are unimpeachable sources of information to aid him if he will seek out these sources

In evaluating testimony is it not useful to know which of the witnesses have studied the industrial environment in question? Does a disease-provoking hazard actually exist? Does the expert witness, who may be a *medical* college professor cloistered in a university hospital, know anything about the plant? The assumption that the industrial physician who spends at least part of his days with the industrial operation and with the workers is ipso facto a prejudiced witness is a pernicious assumption. The industrial physician may have been the one who was instrumental originally in bringing the case before the commission! In my own industrial experience I find that there are more workers I have aided by protecting them from an industrial hazard and by recommending that in-

dividual workers deserve consideration for compensation than there are workers with whose claim for such consideration I could not agree. This is undoubtedly the situation with other physicians in industry.

The relationship of trauma to disease is often a stumbling block in compensation hearings. It is to be remembered that trauma may be related to disease in several ways.

1. *Injury may be the direct cause of disease (e g , a puncture wound leading to tetanus)*
2. *Injury may precipitate symptoms of latent disease (e.g , gangrene following a blow to a foot affected with arteriosclerosis, as in diabetes mellitus).*
3. *Injury may accelerate a pre-existing pathologic condition (e g , varicose ulcers)*
4. *Injury may direct the attention of the patient and of the physician to disease already present and entirely unaffected by the trauma (e g , a burn or bruise on the skin of the breast directing attention for the first time to a tumor which had existed for some time previously).*

In the origin of terms used in pathology a distinction was not always made between expressions describing conditions resulting from trauma, those resulting from disease, and those resulting from aging (degeneration of tissues). Thus the term "inflammation" itself implies no distinction between tissue changes following bacterial infection and tissue changes following trauma. The resulting confusion, while it can be avoided, creeps into compensation hearings.

The tenuous legal concept of aggravation of a disease and mistaking aggravation for merely unmasking of disease may give rise to curious and inconsistent decisions Was the aggravation by occupation a real or merely an assumed affair? The occupational episode often simply contributes to the recognition of existing but unsuspected nonoccupational disease. At plant "Y" in state "X" I have seen two illustrative claims. Worker "A" while drilling as a plant guard in the hot sun sustained an attack of unconsciousness which led to his death It was found at postmortem examination that he had a lung cancer, the cells of which had moved through the blood stream to his brain The cancer in the new location (a metastasis) opened a blood vessel which in turn poured blood into the man's brain bringing about unconsciousness and death The com-

perform, I too have been much concerned with the decisions of some state industrial boards and commissions, *particularly in cases of alleged aggravation.* This concern is prompted by the effect such unreasonable decisions have on the workmen themselves *and on their opportunities for* earning a living in their chosen occupations.

One of the chief purposes of compensation *legislation is to reduce* accidents and to improve environmental exposures which lead to occupational injuries and diseases. The *foreword in the Wisconsin Compensation* Law, enacted in 1911, gives this purpose: "To provide means of minimizing the number of *accidents in industrial pursuits.*" *In* 1919, occupational diseases were added to the legislation for precisely the same reason. Prevention was the goal, which we all agree has been largely achieved, as evidenced by the marked reduction of occupational diseases and injuries in states where such laws have been properly administered.

However, when compensation boards have gone beyond the original purposes of such legislation by ruling unwarranted aggravation of pre-existing disabilities and diseases, industry to protect itself has been forced in many instances to adopt more rigid requirements on physical examinations made before hiring What should be a preplacement examination then becomes a pre-employment examination and all prospects who are not perfect physical specimens are rejected for almost any work. Organized labor, in turn, has protested against such oppressive examination programs by forbidding physical examinations altogether. A vicious circle thereby is set up. Prospective workers no longer can be placed at jobs for which they are particularly suited considering their handicaps, resulting in more injuries and in real aggravation of their pre-existing conditions, with development of permanent chronic disease which usually goes unrecognized until it is too late for cure. The primary purpose of compensation has thus been defeated.

Such a situation places the physician in industry in a very peculiar position. From his experience, he knows that persons with certain handicaps may be placed at certain *jobs with complete safety to themselves* and their fellow workmen For example, he knows that persons with arrested and *healed tuberculous* lesions in their lungs may safely be

disease which has been proved to have an aggravating effect on pre-existing tuberculosis

Yet, if the physician is unfortunate enough to be practicing in a state where numerous other factors have been ruled as having an aggravating effect on tuberculosis, he cannot possibly justify the certification of persons with tuberculous scars for work where they are exposed to such factors For instance, if heavy exertion, extremes of heat and cold, excessive worry, exposure to gases and nonsilicious fumes and dusts have been held to be reactivating factors on tuberculosis, he would be perfectly justified in advising that any person with a tuberculous scar not be hired for jobs having such exposures As every doctor knows, it is quite impossible to be certain that a tuberculous scar is well healed and will never reactivate, no matter how stable it appears on the X-ray film Even persons with sedentary office jobs in air-conditioned rooms occasionally are found to have a reactivated tuberculous lesion which had appeared well healed The Metropolitan Life Insurance Co, which has one of the most complete tuberculosis control programs along with ideal working conditions for its home office personnel, still finds an average of one new active case per 1000 each year

In Wisconsin, where we have had enlightened administration of the Occupational Disease Law, we have allowed persons with arrested and healed tuberculous lesions to work at suitable jobs, i e, at work which is known not to be a silicosis hazard Ex-patients who have been properly rehabilitated are given such jobs just as readily as are those with scars who have not had clinically active disease Our sanatorium doctors have not seen any more recurrent cases than are seen in states where ex-patients are routinely denied employment at all except sedentary jobs

Certain considerations, of course, are essential to such a program, the most important of which is proper medical supervision In plants with a medical department, periodic check-ups and chest films can be made without difficulty In smaller plants, a condition of employment must be that the worker keep himself under the supervision of a qualified physician and furnish the employer with reports of the periodic examinations The important consideration is to protect the other employees against contact with a reactivated worker with a positive sputum, necessitating as early detection as possible of any reactivation

Another result of the enlightened administration of our Occupational

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Such a situation places the physician in industry in a very peculiar position From his experience, he knows that persons with certain handicaps may be placed at certain jobs with complete safety to themselves and their fellow workmen. For example, he knows that persons with arrested and healed tuberculous lesions in their lungs may safely be employed at most jobs not involving a significant exposure to silica dust He knows from his experience and that of others that silicosis is the only

disease which has been proved to have an aggravating effect on preexisting tuberculosis.

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Another result of the enlightened administration of our Occupational

Disease Law is that we are keeping our early silicosis cases at work and are allowing employment of prospective workers with early silicosis in industries which caused their silicosis. As physicians experienced with silicosis know, all persons with first and early second stages of the disease are fully able to carry on at heavy physical labor without undue effort As a result of such a program, we are not relegating to the scrap-heap a lot of perfectly able workers. Furthermore, we are preventing the mental invalidism and neurosis which usually results from the rejection of all workers whose X-ray films show anything abnormal. Our early silicotics are for the most part a satisfied and appreciative group of workers whose production is above the average. They are not developing fancied disabilities and are not filing claims for compensation for their silicosis without a real basis for such claims. Furthermore, in the majority of cases their silicosis has not progressed. Also, in almost fifteen years of periodic observation of from 400 to 500 workers with silicosis, we have found relatively few cases of new tuberculosis superimposed on the silicosis The majority of the silico-tuberculosis cases we have seen develop have been reactivations of pre-existing tuberculous lesions

That this program was sound is shown by the continual decrease in the numbers of silicosis and silico-tuberculosis claims filed with our Industrial Commission in the past ten to twelve years. There, of course, are other causes for such reduction of claims, including a steady increase in general employment during this period as well as the wise decisions of our Commission on uncomplicated silicosis cases. The fact that they have not ruled disability with uncomplicated discrete nodular cases has discouraged much unjustified and unfortunate litigation Nevertheless, we can safely say that our program of hiring silicotics and keeping them at work at least has not resulted in an increase of claims for compensation

Such a program requires certain very definite conditions of employment, chief of which are these:

1. *A safe place to work as far as the dust hazard is concerned.* As increasing numbers of our dusty trades, especially small foundries, have brought their dust counts down to the 5,000,000 particles per cu ft. range, more and more of them can be classified as safe places to work Plants which can qualify for this classification should not be held responsible for aggravation of a silicosis acquired elsewhere. Unless this becomes recognized by industrial boards in their decisions on individual cases, dusty trade em-

ployers not only will refuse to employ workers with only traces of silicosis, but in addition they will lose their incentive to qualify for the safe plant classification.

2. No evidence of tuberculosis in the prospective employee with silicosis. If the preplacement X-ray film shows any evidence of a tuberculous focus in addition to the silicosis, even though inactive, we still advise nonemployment even in plants which we consider safe. This appears somewhat inconsistent, yet it is entirely sound on close study These are the cases which develop into a progressive and disabling silico-tuberculosis regardless of how little further dust exposure they may have. However, since we have no information on how low any additional exposure must be to be considered nonaggravating with such cases, it is safer to advise them to stay away from any further dust exposure
3. More frequent periodic examinations Where dusty trade plants are examining all of their workers every two or three years, those with silicosis should be examined and X-rayed at least once a year This is necessary to detect any increase of the silicosis as early as possible as well as to find any incipient tuberculous lesion before it has progressed too far

The two examples I have given of the results of sound compensation administration can be supplemented by many others which time prevents my mentioning All tend to prove the same thing, i e , that logical medico-legal decisions based on sound scientific analysis plus good common sense thinking lead to increased employment of handicapped persons and their better placement at suitable jobs This in turn leads to more satisfied and productive workers, better working conditions, and fewer occupational injuries and diseases This, I am sure, is what the early framers of compensation legislation had in mind as an ultimate goal

Further Discussion

DR. SAPPINGTON. First, I want to congratulate Dr. McGee on a very excellent paper, not only well prepared, but well delivered. Also, I think Dr. Sander has done pioneering work in the State of Wisconsin, particularly with respect to placement of employees with pulmonary disease, an outstanding piece of work, for which he is to be congratulated.

There are a great many phases of these subjects that Dr. McGee and Dr. Sander both touched upon. One of the things that has always impressed me in compensation hearings is the tremendous mental handicap that is wished upon a claimant when his attorney brings in medical testimony to the effect that he is "permanently and totally disabled." It would seem to me that at such hearings there should be some method whereby the claimant is not subjected to the psychologic handicap of being told repeatedly in the course of the hearing that he has no further chance to be a producing unit in the community, a self-supporting citizen.

There are other discrepancies in these hearings, due to the system, I believe. But I'm sure that most medical men have been tremendously embarrassed when, after having answered a long hypothetical question on direct examination, which is bad enough in itself, on cross examination the attorney for the opposite side asks the medical witness to assume exactly the opposite position in regard to the things that he has already answered on direct examination.

Now, as I say, this is part of a system. I don't know what can be done about it, but it seems to me that is one of the things that should be given attention. I know that there are bodies, the International Association of Industrial Accident Boards and Commissions, for example, that are now working on procedure. One of the things that should be done is to get a great deal more coordination of effort between professional witnesses and the administrators.

MR. WATERS. Thank you, doctor. May I ask Dr. Cranch of the Union Carbide and Carbon Corporation to say just a word.

DR CRANCH. I have very little I can offer that would be more concise than what Dr. McGee presented. It was an excellent resumé.

There are just a couple of observations that might bear on the subject. When it comes to compensation of occupational disease there was a time when I thought that the schedule method was the best, in that it precluded the inclusion of a lot of irrelevant illnesses, but as time goes by, it is evident that this is not completely true. It comes back to the question, what is a proper definition of occupational disease? With that it then rests with the Commission to interpret the laws themselves

But the definition of an occupational disease is something which should be given considerable thought. There is a tendency in some jurisdictions

to take more or less the attitude "the man is sick, isn't it possible to get him sickness compensation under the law?" And they will do hand-springs and somersaults in order to give him compensation, which is rather unfortunate.

What seems to me the best answer to that situation is the more general use of competent medical referee boards who are not beholden to either the employer or the employee, but are employed by the Commission as an impartial, competent source of medical opinion for the guidance of the Commission in making decisions. With such boards properly constituted and free from political influence, and their findings properly evaluated by the administrator, I think there will be very little difficulty.

That brings us back to another related problem, the theories in regard to the aggravation of a pre-existing condition I think such cases are very loosely evaluated at times. You are actually penalized for giving work to a man entirely capable of carrying on a certain kind of work because, if he dies of that condition, you "hold the bag."

I know of a case of a diabetic who was known to be diabetic, he knew, the employer did, the physician did The poor chap could do something, but not very much, and his physician gave him just a few months at most to live—so they let him stay around One day he came in reporting a black toe, and on examination it was found to be diabetic gangrene It was suggested "Didn't you bump that?" His job was cleaning out rubbish around the office. He said "Perhaps I did bump that toe against the desk when I took the waste basket out a couple of days ago." His employer had to pay a complete death claim because of an injury suffered during occupation, "with aggravation of a pre-existing condition"

But until somebody is able to evaluate such cases and give them their proper weight, it's going to be difficult to administer the law in some of these instances with any fairness It has been brought out that the mental effect on the other employees is very bad when they see how distorted the decisions are in some instances

Then there is the influence of trauma on disease There is the tendency to claim that certain conditions aggravate disease sometimes with very little basis at all. We should give more consideration to the probabilities in judging these cases I would like to see more and better boards of medical referees to help evaluate medical testimony

MR. WATERS: Thank you, doctor. I happen to see the Chairman of the Medical Board of the State of Maryland, Dr. Nathan Herman. Would you be kind enough to say a word on this subject, Dr. Herman?

DR HERMAN: The question of whether compensation for occupational diseases should be according to a general broad coverage really seems to me to be rather immaterial, depending primarily on the administration from the standpoints of fairness and of general applicability. And that brings us up squarely against the question of how such cases are judged. I agree entirely with Dr McGee in being conditioned by my own experience, that brings us squarely against the question of diagnosis.

Of course, doctors aren't infallible, but they certainly will be in a much better position to arrive at an adequate diagnosis than a lay board. If legal means can be found to make such medical opinion stick and be final as medical facts—and I want to emphasize medical facts—I think a broad coverage will certainly be advisable.

Unfortunately, we're all beset by the bugaboo of respiratory disease in occupation and that goes all the way from simple colds to pneumonia. I don't think that will present too great a problem—again, provided medical opinions prevail.

However, where such opinion is going to be subjected to the caprice of a lay body, then I foresee great difficulty in administration

I think Dr. McGee might very well have expanded on the question of training of physicians in the recognition of occupational disease I am sure he would have, had time permitted. Certainly, in our experience, that represents one of the chief difficulties in that we get simply inadequate recognition of occupational diseases. If such claims are held before medical boards, I think that you will do away practically entirely with ex parte medical testimony and render entirely useless the whole question of referring medical testimony to a board of censors.

If these cases are heard before a medical board or a board of medical referees or any other such device, and that board over a period of time will express its opinion concerning ex parte testimony—as we very strenuously do we simply want to hear the testimony of a physician, preferably a qualified one, rather than "your" physician and "my" physician—then we will certainly be in a much better position to evaluate the testimony and to have a clear record of what goes on.

CHAPTER 35

Viewpoints of Workmen's Compensation Administration as to Occupational Diseases

HON. MARY DONLON*

It is the responsibility of administration to make do with what is available, as effectively and efficiently as possible, and to strive constantly to devise something better. What workmen's compensation administration presently has to do with, in cases of industrial disability caused by occupational disease, creates problems that are somewhat different and more difficult than workmen's compensation administration usually encounters in traumatic disability cases This derives chiefly from a lag in legislation, which in turn reflects a lag in medical science in the field of occupational disease

In workmen's compensation, administration at best functions under the handicap of legislation that is peculiarly technical and diffuse, usually a patchwork of frequent and sometimes unrelated and even contradictory amendments Workmen's compensation legislation has been evolving hesitatingly over a period of nearly four decades But workmen's compensation legislation in the field of occupational disease has evolved even more uncertainly and slowly than has legislation with respect to accidental injuries.

The reason is fairly clear All social legislation derives from an informed public opinion Long after public opinion, in most states, had won statutory recognition of the principle that industry should fairly be held liable for its accidental casualties, there still was lacking the public opinion and public leadership necessary to achieve equal statutory recognition for the industrial disablements that are caused by a wide variety of occupational disease hazards The fast moving chemical and

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technologic developments reflected in modern production processes required fast moving developments in industrial medicine Understandably, but unfortunately, industrial medicine did not keep pace. This modern branch of medical science, developed to cope with the diseases caused by deleterious industrial processes, has not received even yet the public and professional recognition necessary for support commensurate with its social and economic importance.

Yet workmen's compensation administration necessarily must look to an informed medical profession (and under free choice that means to the local practitioner) for diagnosis that will at least suggest to administration the correct causal relation of disease to an industrial exposure The etiology of many industrial diseases is still obscure. Moreover, the considerable body of such medical knowledge presently available is in the possession of a relatively small group of medical scientists and scholars. Not many of the physicians regularly practicing in workmen's compensation cases are in this group. The neighborhood doctors who see and treat most ailing workers often fail to identify illness as an occupational disease Moreover, they frequently lack the informed curiosity that would seek promptly the complete history of the patient's occupational exposures Without such history, correct diagnosis is sometimes almost impossible. Certainly the lack of occupational history has delayed, in workmen's compensation proceedings, proof of the causal relation between disease and employment necessary for the award of benefits to disabled workers Conversely, indiscriminate diagnosis inaccurately relating disease to occupational hazards often gives rise to palpably false hopes as to compensability and puts an unnecessary and serious burden on administration

It is undoubtedly true, also, that many workers annually lose workmen's compensation benefits to which they are fairly entitled, either because their illness is never identified as industrially caused or aggravated, or is so identified so tardily as not to allow claim filing within the statutory period of limitation.

It would be pure speculation to estimate how much costs are increased because patient care suffers from inaccurate diagnosis, while at the same time fellow workers and their employers continue unaware of the seriousness of an identifiable industrial hazard. It must be a considerable cost, both in avoidable human suffering and in dollars.

What are current viewpoints of workmen's compensation administration with regard to occupational disease? I can speak only for workmen's compensation administration in New York State, but the recent volume of correspondence and a steady stream of official callers from other states and foreign countries, inquiring as to the New York Workmen's Compensation law and administration, bespeak a widespread postwar concern in this important industrial and social problem. That interest is confirmed by this symposium, participated in by the medical profession, government officials, management, labor, and insurance companies

With the single exception of the dust diseases, the New York law for ten years has provided unlimited all-occupational disease coverage without discrimination, as to medical care and cash benefits, between disease disablements and traumatic disabilities The current viewpoint in New York as to the dust diseases is that, so far as workers are concerned, the ten-year-old discrimination should be eliminated In agreement with this viewpoint, the New York Legislature passed in 1947, and Governor Dewey signed, a significant new dust disease law which became effective July 1, 1947 This 1947 legislation repealed Article 4-A of the Workmen's Compensation Law, the old statute that had limited benefits payable for disablements and deaths caused by the dust diseases The new law lifted the ceiling from aggregate benefits payable in death cases and for total disablements caused by silicosis and other dust diseases At the same time the Legislature appropriated $50,000 for research and study in the evaluation of partial dust disabilities and that important research is now proceeding here at Trudeau Foundation It is a story in itself, and one that we all hope will soon have a satisfactory ending

Two principal problems plague all who are concerned with workmen's compensation for silicosis and other dust diseases How should partial disablements be rated? And who is to pay? New York, as the result of the scientific research and study now undertaken, hopes that a tenable basis for rating partial dust disablements will be found, and soon. The problem is, medically, certainly far from easy The relationship of disease progress to actual work disablement in silicosis and other dust diseases seems to be unpredictable Functional effects may vary so widely among workers who have been subjected to like exposure, and even as to workers whose X-ray pictures reveal comparable lung involvement, that determination of the proper basis for evaluating and equitably compensating

partial disabilities has sometimes been guesswork, unsatisfactory alike to workers and to employers. This medical difficulty is, of course, not a valid excuse for doing nothing New York is definitely doing something in this matter of evaluation of partial dust disease disabilities, and what New York is doing by way of research in functional tests promises significance for other states as well

The second seriously troublesome question is which of several successive employers should be required to bear the cost of workmen's compensation in dust disease cases. Disablement or death of a worker often follows exposure to dust hazards in numerous jobs for different employers, usually over a considerable period of time. When the ceiling was removed from dust disease awards, giving workers benefits throughout their continuing disability and dependents benefits throughout dependency, should the last employer in an exposed employment be charged with the entire workmen's compensation cost of a total disability or death? If so, and notwithstanding all possible safety precautions, might not such a heavy burden of cost bring about discrimination in new employment opportunities available to workers in the dusty trades?

The cost in New York of compensable claims is not a negligible item. Benefits are high The maximum weekly disability rate is $28, and benefits continue during work disablement, without the statutory ceiling on aggregate liability that is characteristic of the workmen's compensation laws of many states and countries. Similarly, in death cases, the employer is liable for payments to the widow through widowhood, to the children until they are 18 years of age, and to other dependents during dependency. That is obviously a fair provision for the workers, but the cost to an employer is considerable The average value of cash benefit awards in all permanent total disability cases closed in 1946 by the New York State Workmen's Compensation Board was $18,679. The average value of cash benefit awards in 1946 death cases was $7,207. New York employers are required to pay necessary medical and hospital care of disabled workers, and the considerable cost of such care is not included in these figures It is a substantial extra cost.

Should the last employer pay all, even when the disabled or deceased worker had previously worked for other employers in dusty employments?

Convinced that there should be no discrimination in benefits among workers who are disabled by the different industrial hazards, the prob-

lem of incidence of employer liability was met in the 1947 New York State dust disease legislation by an ingenious and novel use of the Second Injury Fund

It will be recalled that in New York the Second Injury Law, since 1945, has been unusually broad It is not limited to injuries involving the loss of a second member or eye, as in most jurisdictions, but extends to all cases of industrial injury, including occupational disease, that result in substantially greater disability due to the worker's previous permanent physical impairment Moreover, the Second Injury Fund in New York does not depend for financing on occasional assessments or fee collections, but is financed through annual pooled carrier contributions This financing, being outside the rate experience of individual employers, is spread on industry as a whole.

The new dust disease law which became effective in New York on July 1, 1947, imposes on the last employer in an exposed employment liability for workmen's compensation benefits only during the first five years, in cases of total disability and death, and the balance of liability is charged against the Second Injury Fund (The single exception is in the case of deaths occurring on or after July 1, 1947, following a compensable total disability prior to that date, in which case the charge on the individual employer in the death case is for the benefits during the first two years) By this device, workers get full workmen's compensation benefits, but a substantial part of liability in dust disease cases is transferred away from individual employers to industry as a whole

This seems eminently fair, because industries in which dust is prevalent—mining, steel mills, stone crushing, ceramics, foundries, to mention only a few—supply basic goods For instance, 85 per cent of all manufactured goods in the United States are reported to contain steel in one form or another Through this transfer of liability to the Second Injury Fund experienced workers in the dusty trades find new employment opportunities, as they might not if the last employer risked unlimited workmen's compensation liability

The time of disease contraction in the dust diseases was extended, in 1947 legislation, from one year to two years after last exposure, and the former five-year limitation in death cases was removed from the law.

Repeal of the "ceiling" or statutory maximum for benefits prescribed in old Article 4-A has the important administrative advantage of eliminat-

ing the occasion for controversy as to whether a disablement is properly to be classified as a dust disease or as some other occupational disease. Except *in partial disabilities, there is no longer any basis for such controversy.*

War production processes drew the spotlight of attention to the so-called slow starting or *latent developing diseases. Administration became* increasingly aware of the hardships inherent in a statute of limitations that barred benefits to disabled workers whose occupational disease was of such a nature that it seldom or never caused disablement as early as one year after last exposure.

In 1947 New York made significant progress in relaxing the statute of limitations, providing a special and more realistic statute as to occupational diseases which cause latent or delayed pathologic bone, blood, or lung changes or malignancies due to exposure to or contact with arsenic, *benzol, beryllium, cadmium, chrome, lead, or fluorine, to air pressure, or* to exposure to X-rays, radium or radioactive substances, in all of which it is recognized that objective symptoms develop slowly

Under the new law which became effective July 1, 1947, in New York State, a worker whose disablement is caused by one of the enumerated *diseases is permitted to file his claim for workmen's compensation bene*fits and to give notice to his employer, within ninety days after disablement and after knowledge that his disease is or was due to the nature of his employment, notwithstanding the lapse of more than the usual short statutory periods of limitation with respect to notice, claim filing and the period previous *to disablement within which the disease was* contracted

Where the death of a worker is caused by one of these slow developing diseases, and no claim was filed or determination made with respect to his disablement prior to death, benefits will be awarded to his dependents in cases where causally *related death ensued within five years after* contraction of the disease Where before death a compensable disability had been claimed or determined, the usual period limiting death claims is, of course, entirely fair

It should be observed that this new legislation was drafted a year ago, and was introduced in the *New York Legislature in January 1947,* before public attention had been widely directed to some of these occupational hazards, such as beryllium which has been the subject of discussion dur-

ing the first four days of this symposium This legislation is a splendid tribute to the progressive interest of New York State in sound and forward looking workmen's compensation measures There is no counterpart of this law in other States It breaks new ground in occupational disease legislation and opens new frontiers to workmen's compensation administration in the development of medical evidence and the adjudication of claims based on pathologic bone, blood, and lung changes and malignancies caused by the enumerated exposures

Workers who have been temporarily disabled by occupational disease sometimes find, upon recovery, that medical opinion opposes their return to the old harmful occupation This is notably true where the worker suffers from an allergy that is irritated by an exposure in that employment To facilitate the rehabilitation of such workers into an employment free of the noxious hazard, the New York Workmen's Compensation Board has power to find a partial disability in such cases Where the Board finds that a worker is able to earn wages in an occupation that is neither unhealthful nor injurious, but in which the wage does not equal the full wage earned prior to disablement, the Board may award workmen's compensation benefits on the basis of reduced earnings

The broad scope of the Second Injury Law in New York State has been mentioned It embraces disease either as a first or second injury, or both. This has done much to make the "over 40" age group employable in New York State When workers afflicted with chronic diseases that limit their employment opportunities, such as cardiac ailments or arrested tuberculosis, contract an occupational disease or sustain an industrial accident that results in permanent disability caused by both conditions materially and substantially greater than would have resulted from the occupational disease or industrial accident alone, the claims come under the provisions of the Second Injury Law.

Because the theory of compensable disability through aggravation of a pre-existing condition had already been judicially confirmed in New York, this new law does not add anything to the amount of benefits disabled workers receive They already received full benefits What the new law does change is the incidence of employer cost By transferring to the Second Injury Fund the liability in excess of the first 104 weeks in these permanent disability cases, the cost of workmen's compensation to an individual employer is so reduced that he need no longer hesitate,

in New York State, to employ qualified workers with partially disabling physical impairments. The social values of this forward looking workmen's compensation legislation are tremendous. The notable gain to the labor force is equally important to the nation's production effort.

Current viewpoints of workmen's compensation administration in pulmonary and other occupational diseases, as they appear to administration in New York State, may therefore be briefly summarized as follows:

1. Benefits to disabled workers should be no less for an occupational disease disablement than for a traumatic disability.
2. The medical characteristics of certain latent or slow starting diseases call for a realistic period of limitation not measured from last exposure.
3. The burden of workmen's compensation costs may be a serious deterrent to the employment of workers who in previous employment have been injuriously exposed to hazards that cause progressive deterioration, as in the dusty trades Spreading excess workmen's compensation costs to industry as a whole improves employment opportunities.
4. Similarly, the middle aged and older workers, and those of all ages who have permanent physical impairments, are more readily employable when excess workmen's compensation costs per second injury or occupational disease are lifted from the employer and transferred to a Second Injury Fund
5. Rehabilitation of workers who would be harmed by return to an occupational exposure calls for payment of workmen's compensation benefits until earnings in a medically safe new employment equal those in the medically unsafe old employment

The cooperation of the medical profession at every level is urgently required for the satisfactory administration of workmen's compensation in cases involving occupational disease. Expert consultants are usually available, at least in the large cities, to give to workmen's compensation administration specialized and competent diagnosis, prognosis, and opinions on causal relation and treatment They cannot, obviously, advise workmen's compensation administration about those cases that are never identified as occupational disease disablements by local practitioners, or are so identified too late

There is, moreover, urgent need for the establishment of suitable and

generally accepted standards in such matters as laboratory examinations and X-ray pictures of affected areas. It is well known that X-ray pictures are not always accurately revealing of controverted conditions as to which expert testimony is required Pictures may and often do fail to reveal the true pathologic condition, and this failure sometimes results in gross miscarriage of justice and certainly in serious delay There is this same need for accepted standards in laboratory examinations, so that accurate reports may be available to workmen's compensation administration when, as so often happens, the results of a laboratory examination are the only evidence, long afterward, of conditions on which proof of causal relation may rest.

Meetings like this, devoted to exploring and spreading medical and medicolegal knowledge of the obscure occupational diseases, are of great value to workmen's compensation administration More such are needed

There is need, too, for more emphasis on industrial medicine in medical education. In this country we might well profit from the experience of Switzerland, where for years industrial medicine has been a required subject in the curricula of all medical schools In an era characterized by increasing industrial exposure to substances the hazards of which are unknown, or understood only in part, or known positively to be harmful, the sound administration of workmen's compensation, including rehabilitation, requires that the frontiers of medical knowledge be advanced to match the advancing frontiers of industrial technology A society whose survival is dependent on possession and use of the most modern processes of industrial production, requires for survival also sound medical knowledge as to the hazards inherent in those processes

Discussion

HARRY A. NELSON*

The Wisconsin commission has taken especial interest in the subject of occupational disease since inclusion of occupational disease under the Workmen's Compensation Act in 1919 At that time the disease which gave the commission the greatest concern was that of silicosis, either with

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or without tuberculosis. In order to obtain the best information available on the subject a conference was called by us at Chicago in November 1932, and noted specialists in their fields were invited to attend. The conference lasted for two days, during which the subject was thoroughly explored. Much additional knowledge has become available since that time.

Following the Chicago conference the late Dr. Gardner was persuaded to conduct a similar symposium at Saranac Lake, which was held, I believe, in 1934. We in Wisconsin like to believe that the Saranac symposiums were initiated because of the Chicago conference. From these symposiums we have learned much We cannot let this occasion go by without complimenting the Saranac Laboratory, and those who are instrumental in arranging the symposiums, for making available to boards and commissions information on various occupational diseases, particularly silicosis and tuberculosis

In Wisconsin all manner of mental and physical harm arising out of employment is compensated without schedule and regardless of type. We believe that above all types of injury occupational disease should be compensated That is because the employee usually has little or no control over the hazards which cause these diseases. He can, to a large degree, prevent accidental injury That is not true as to occupational disease We have always thought that there should be blanket coverage, and that states should not, because of timidity and fear that they may not be able to "cope with the problem," exclude many diseases and conditions, even though cases may be difficult to decide. As a matter of fact, the Wisconsin experience has been that cases of occupational disease are no more difficult to decide and in some cases easier to decide than are those of accidental injury Certainly the question of causation of disease as related to accidents of various sorts presents at least as much difficulty.

We all agree that cases should be decided on a scientific basis and not merely because of sympathy or by hit and miss methods. Compensation administrators are usually laymen as distinguished from persons who have been medically trained Many administrators do not have doctors on their staff The best medical opinion should be available to all administrators. The work which has been done here at Saranac Lake and the symposiums which have been held from time to time have been of inestimable value to administrators throughout the country. They have

been enabled to learn where the scientific truth lies, and thus to reach intelligent and factual decisions of compensation cases.

I believe doctors should always be cautioned that the test in workmen's compensation, at least in the great majority of states, is that of probable connection rather than absolute unquestioned causation as between work done and disability which becomes apparent. We often hear of a doctor who has testified as to probable causation by employment asked whether he can positively state that the condition resulted from an accident or from exposure at work. He may answer that he cannot so positively state The question then follows, "Then your opinion is based on conjecture?" The doctor then answers that he supposes that is true. Some administrators may then be prone to hold that the claimant has failed to sustain the burden of proof, and from the legal standpoint that is probably correct Both administrators and doctors should have in mind that the test is one of probability rather than of certainty, and that when reasonable probability is shown, liability should be found. That test is of the very essence of the liberality which should pervade compensation administration and procedure

We cannot too strongly stress the necessity for pre-employment and interim employment physical examinations of employees. It is of vastly greater importance to prevent disease than it is to provide for compensation after the disease has occurred Prevention can be attained only by a knowledge of the employee, the conditions under which it is proposed that he work, and an intelligent placing of the employee in an environment which will not be dangerous to him and to his fellows How can that be done without knowing the employee's condition? How is it possible to prevent disease if we permit the exposure of one who already has a condition which renders him unduly susceptible to that disease if exposure to deleterious substances occurs? But unless the practice and use of physical examinations are carefully safeguarded, employees are properly going to refuse to submit to examinations Many enlightened employers do not need the force of law in order to prevent discrimination against those with physical handicaps Many employers are intelligently examining and placing these persons in service rather than excluding them from service—always, of course with the sort of intelligent and discriminating placement which will insure safety to all concerned. Some employers are not so enlightened We must, therefore, have rules and laws which will

make it expensive for the employer who intends to take unwarranted advantage of physical examinations, either before or during employment

What is the doctor's function in connection with industrial disease? If he is going to be able to give intelligent reports and testimony as to causation and extent of disability as related to occupational exposure, he must inform himself. He must not only inform himself but he must, as our people in Saranac Lake are doing, see that scientific information is produced and published which will enable doctors generally to have correct information. It is then his function without fear or favor, to give the scientific facts to the employer, the insurance carrier, and to the compensation administrator without regard to the question of what the result of his testimony may be when honestly and competently given. No doctor should give an opinion which is tinctured with the question of whether the result from the doctor's viewpoint is good or bad. The doctor is concerned merely with scientific opinion and fact. When he has given these honestly and scientifically, it is the administrator's function to apply the law and to decide whether the result is not good or bad, but in accordance with the law of his jurisdiction It is for the legislature to decide as to whether the result is a good or a bad one Too often we hear it commented that if a case is decided in a certain manner the result will be bad for labor or for industry. Curious decisions are reached when that sort of rationale is indulged by the administrator.

Above all, the finest attainment achieved by study of occupational disease is prevention and elimination, to a large degree, of the disease involved Wisconsin is proud to say today that silicosis has been nearly stamped out in our state because of the outstanding work which has been done by employers, insurance carriers, safety people, and public agencies in Wisconsin That is true, to a large degree, of lead poisoning. It is one of the most hopeful and finest accomplishments which can be envisioned to know that as disease can be traced to employment, the ingenuity of doctors, engineers, and others concerned rapidly comes forward with effective means of eliminating and preventing disease, and thus carrying out the most important objective of all—the saving of life and limb and the prevention of human suffering and distress.

One subject which we believe is deserving of especial attention is that of a finding of partial disability in a case where the employee is able to continue at work. This is sometimes known as medical disability Persons

with silicosis, we think, should be kept at work, provided they are able to continue at work which they are able to do—provided a safe environment can be afforded. We believe that persons with first and second stage silicosis should usually continue in employment, first, because the facts show that they are not actually disabled in many cases, and second, because discharging them does not improve the situation It loses for the employer employees with great skill, it stigmatizes the employee who may have difficulty in procuring work from other employers, and it creates a neurotic condition, which is highly undesirable On the other hand, there should be protection for the employee who has accrued disease, and who, if discharged, may thereby suffer wage loss, even though physically he is able to continue work and it may be safe for him to do so. Wisconsin has a provision for payment of up to $3500 for nondisabling silicosis resulting in discharge of the employee and consequent wage loss That has resulted in retention of employees in service which is safe for them and their fellow employees, and economically in savings for both employer and employee Inherent in this sort of procedure is the necessity for repeated medical examinations, so that if at any time employment is shown to have reached the point of danger, the employee may be discharged and be paid compensation for the wage loss which results from his condition.

Further Discussion

MR. WATERS Thank you, Mr Nelson This paper is now open for discussion. I believe that Dr Vidal of the Quebec Commission is in the audience If that is correct, I would appreciate a remark from him

DR VIDAL I'll do my best, but it's easier for me to talk in the French language I am quite sure that if you understand my English, you must be very intelligent

In the Province of Quebec, we compensate partial and permanent disability for silicosis if the claim is submitted to the Board within five years, and even thereafter the Board of Commissioners may accept a claim for medical expenses if they find some reason to justify the decision.

The two main questions in our province are (1) prevention of the disease and (2) evaluation of the degree of disability We must agree that we cannot do much in the treatment, we are still awaiting the

thus find them lying around in the town without adequate means of support.

May I ask what, in Wisconsin, where the insurance scheme seems to be very efficient, is done in such a case? Is the man compensated when, let us say, he presents a condition of mild silicosis and, at the same time, of tuberculosis? Is he paid full support during his stay in the sanatorium?

DR. SANDER: Yes. Any case in which silicosis with active tuberculosis is found, no matter to how slight a degree, if it can be diagnosed by X-ray, is considered a compensation case against the last employer who contributed a significant dust exposure The insurance companies or the self-insured employers pay for the sanatorium care, as well as the compensation.

MR. WATERS. Any other commissioners in the audience?

DR. MAYER. I happen to be one of those who have fallen for the charms, the "charmed profundity" shall I say, of Mary Donlon, and also for her keen insight and wisdom in this field of compensation industrial medicine. I am one of the members of a board of three pulmonary consultants in her division of New York State Dr Amberson, Dr. Whipple, and I constitute the board. We see the disputed cases. Only rarely do we find that physicians will fully give opinions that are not their best.

We find diseases complicating dust inhalation, such as cardiovascular disease, where it is often impossible to evaluate the major factor in disability, and where only on repeated examination can one accurately define causal relationship.

I mention this because it is the impression that many physicians regularly perjure themselves in testimony

MR. WATERS Any commissioners from other states here who'd care to say a word? Any other questions you gentlemen might care to ask, we'd be glad to have them.

DR. VOSBURGH. The question of silicosis and tuberculosis poses an interesting problem, when one sees tuberculosis without any demonstrable silicosis in a worker who is potentially exposed to some degree of silica dust. I'd like to know how those cases are handled. Let's assume the presence of tuberculosis in a short-term worker, say a worker in a foundry or in some occupation where he has a definite but limited exposure to

such dust, when some demonstrable silicosis is not present in the lungs—just pure tuberculosis, as far as anyone can determine

MR. NELSON If there is not sufficient silicosis so it could be said it had some part in developing the tuberculosis, no liability would be held When a short-time worker has exposure to silica and develops tuberculosis, then the question comes up, is the exposure so negligible that we can throw it out as a factor, or find that, because of previous exposure, it falls to a prior employer, rather than to the last employer.

MISS DONLON I think I might agree with Mr Nelson in the main in his remarks about the Wisconsin law, with this exception, that in New York State tuberculosis in itself is an occupational disease In the nursing profession, tuberculosis not complicated with other factors is a compensable disease In general, in industry it would relate to all the medical factors substantially as Mr Nelson has outlined them

CHAPTER 36

The Insurance Viewpoint

HENRY D SAYER*

In accepting the invitation to speak on the subject of occupational diseases from the insurance viewpoint, I stipulated that I could not state any conclusions with authority that would seem to express the accepted view of the insurance industry or to commit that industry to any course of action To speak with any such assumed authority is not my function, and surely the spokesmen for the stock company interest and the mutual company interest are far better able than I to state the views of their respective groups. Moreover, state funds that have been set up in many states to insure the obligations of employers under compensation laws will also have their own individual points of view, as to which I do not speak Insofar, however, as my knowledge and experience of the subject may aid in clarifying the relationship of insurance and occupational diseases, I am very happy to set forth my individual views

It is perhaps an unwarranted assumption that insurance, as such, has a special or particular point of view on the subject of occupational diseases Certainly, I do not assume that it has Insurance performs a service of vast importance in making possible the carrying out of the purposes and securing the payment of the benefits of workmen's compensation laws It is not too much to say that without effective insurance and the implementation of compensation laws by insurance principles, the whole compensation system would be weakened to the point of utter impotency If no security for the continuing payment of compensation benefits existed other that the ability of each individual employer to pay not only the immediate benefit, but to continue payments to the satisfaction of the extreme liability imposed upon him, which may extend for years into the future, our compensation laws would become a travesty

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and no worker could afford to accept employment from any but the most financially strong employers Such a result would be utterly crippling to our entire economy

To the extent that our compensation laws play a vital part in our social and economic life, insurance has served, and will continue to serve, an essential interest in our industrial system We take pride in the fact that insurance has taken over, and will continue to take over and relieve the financial obligations of any employer under the compensation law, and will satisfy to the fullest extent any lawful requirement imposed by that law on the employer In doing so, it performs a public service in a high degree In that view of the matter, it is of little consequence to insurance, as such, what the coverage under the law may be It is sufficient that the obligation is insurable, that it is sufficiently definite and described to permit the setting of reasonable and adequate rates, and that it is expressed in definite and certain language so as to be readily understood by those affected by it, and to warrant fair administration and the avoidance of wasteful litigation

It is difficult to think of anything that contributes in greater degree to a lack of respect for our laws than the use of language in an important statute that lends itself to a lack of understanding of rights and obligations, with consequent disappointment on one side or the other when the courts have been obliged to interpret the law and to state the rights and obligations other than as they had been assumed to be

While it may be assumed that the original purpose of compensation statutes was to cover only disability and death due to injury by accident, possibly because injury to health gave no right of action against the employer under the old common law, no one can logically disagree with the principle of compensation for those diseases that are as definitely occupational as are industrial accidents In many jurisdictions diseases to be compensable under the law must be due to causes and conditions characteristic of and peculiar to the occupation For example, every one of the multitude of diseases described in the twenty-seven paragraphs of the old New York schedule will be found to meet that test It is, of course, perfectly logical to include any disease that meets those legal criteria

It is not correct to say that insurance has opposed the principle of compensation for occupational diseases Certainly, here in New York, it

is not so. It is within the speaker's personal recollection that when the first definite occupational disease law was passed by the Legislature of New York State in 1920, insurance contributed information and facts in regard to the meager knowledge at that time of occupational disease and assisted, in accordance with requests of authorities in this State, in the drafting of that first law, which became the model for occupational disease legislation in a number of other states. Industry and insurance joined in urging passage of that law by the Legislature. What insurance has urged in various places and on various occasions was that the occupational disease laws be drawn with such directness and explicit terminology that there be a correct understanding of the rights and obligations created so that there could be little room for litigation. New York State did not in its original law accept the principle of an all-inclusive law, drawn in such loose terms that it might be difficult, if not impossible, to confine its coverage to real occupational diseases, as distinguished from diseases of ordinary life that might by some specious reasoning or speculation be ascribed to a condition or incident in the employment. In fact, New York State, in the opinion of many, has not yet given its explicit approval to the inclusion of coverage in mere broad and vague language for all diseases of every nature occurring to workers. Our first law, enacted in 1920, was what is commonly known as the schedule type of law. It listed all diseases or exposures leading to disease together with a description of the covered employments The schedule then adopted was, as experience developed, very greatly broadened until it covered virtually every recognized disease that was at the time definitely attributable to occupation. In 1935, however, the law was amended to make it all-inclusive, not by striking out the schedule of diseases and substituting some general all-inclusive phrase, but by retaining the schedule and merely adding, as an additional item in the schedule, coverage for "any and all occupational diseases." It may be assumed, therefore, by the application of the legal doctrine of *ejusdem generis*, that the Legislature intended to apply the all-inclusive phrase to diseases having the general attributes and characteristics of the manifold diseases listed in the schedule Unless it was intended that the limiting and defining nature of the schedule was to be observed, what could have been the purpose in retaining the full and complete language of the schedule? The Legislature cannot be supposed to have used language without purpose or

understanding, and the courts will give effect, if at all possible, to all language used in a statute.

It is, however, as I have suggested, a matter of public policy for each individual state to decide whether it will or will not include occupational diseases within the coverage of its compensation law, and whether it will include a general all-inclusive form of coverage or the more definite and exact form of coverage by a schedule or listing of diseases and related occupations, definitely related to the industries and needs of the particular state That public policy will in large measure be informed by the needs and requirements of the people and industries of the particular state, having regard, of course, to the experience of other states and general medical knowledge Labor and management should, of course, have a large voice in the determination of those questions

We are not particularly concerned, at this gathering, with those diseases and infections that follow naturally and unavoidably from injury caused by accident, we are concerned rather with those diseases that result from conditions in the employment caused by exposure to or contact with toxic substances, radioactive emanations, exposure to dangerous dusts, gases or fumes, or other conditions necessarily present and characteristic of a particular employment More particularly are we here concerned with those diseases affecting the lungs and respiratory tract.

The greatest difficulties have been encountered in the consideration of silicosis and asbestosis as occupational conditions While diseases of the lungs, due to inhalation of dust, have been recognized from the earliest times and have been referred to in the ancient literature, until recent years little was scientifically known of their pathology, etiology, and therapeusis Medical science in recent years, especially under the inspired leadership of Trudeau and of Gardner, has made great strides in research and the determination of the facts as to the nature and development of these diseases Not only, however, did the lack of definite knowledge and understanding of pneumoconiosis lead to difficulty in administratively dealing with those diseases and the determination of legal rights growing out of them, but the very slow and gradual progression of such diseases in individuals over long periods of exposure to harmful dust introduced very complicating elements especially from the insurance point of view. During the intervening years, while a worker is being exposed to dust and very slowly acquiring pathologic changes that may or may not

eventually result in his disablement or death, he may be employed by a number of different employers, or have off and on employment by the same employer, and in these various employments conditions may be very different and the character and concentration of dust may widely differ His employments may not all be within the same state and may be governed by different laws or by no laws. His employers may be insured by different insurance carriers and, indeed, even though he work continuously for the same employer, that employer may be insured by different carriers during various periods in the course of his employment. Generally speaking, *the right to compensation arises only when disability*, causing loss of earnings, takes place. The right to compensation having been established, the worker or his dependents are concerned only with the receiving of the benefits set forth in the law, and have no particular concern with respect to the liability for such payments.

Complications of like kind arise when the law, creating the liability *for benefits, is of more recent existence than the period of exposure from which the condition arose. Thus a period of total disability may arise* within a very brief period after the enactment of the new law, while the period of exposure out of which the disease arises may practically all antedate the law creating the liability Here then a condition may arise for which liability is newly imposed by law, but the conditions out of which the disability arose may be wholly or in large part due to conditions of employment at a time when the law created no liability upon the employer or his insurer for such a disability.

Recognizing these manifest facts, the New York Legislature accepted certain very important principles in enacting the law with regard to the pneumoconiosis, namely, first, that the liability for compensation shall be imposed wholly upon the employer who last employed the worker in a dusty employment, and, *second, that the liability for silicosis or asbestosis* under the new law shall be, in the beginning, merely nominal or minimal, taking little account of the exposures in employment which took place prior to the law's enactment, the benefits and the liability therefor increasing automatically as the passage of time and the period of exposure under the new law lengthens. These increments may attach monthly, as in New York, or they may be annual or at other periods, but eventually the benefits reach the full limit of the law. This type of law has sometimes been referred to as the "sliding scale of benefits" or the "escalator clause."

From the time when full benefits are reached there is no diminution of benefits and no lessening of full liability therefor

By fixing the liability on the last employer in a dusty exposure, there is avoided endless difficulty in attempting to assess upon each employer by whom the injured person was employed his proportion of liability for the entire condition This would be manifestly an impossible task. By always assessing the liability on the last employer, the principle of distribution of cost brought about by insurance makes such procedure fair, and it averages out fairly

By utilizing the sliding scale of benefits in any new law, not only is the burden of cost upon industry for accrued liabilities that arose prior to the law's enactment relieved, but employment is made easy The so-called "accrued liabilities" are not insurable, any more than a house is insurable when it is half burned down, or any more than a person suffering from an incurable disease is insurable under a life insurance policy

A somewhat different and very complex question is presented in the matter of compensation for partial disability from silicosis or asbestosis At a superficial glance, it might be assumed that partial disability should be compensated in the dusty trades the same as it is in the case of injury due to accident. But upon slight reflection, it will be recognized that a very different situation must be faced

In the first place, just what do we mean by "partial disability" in dust disease of the lungs? Having in mind the infinitely slow progressive nature of the disease, at what point does it become partially disabling? And how is that disability to be measured? Do we think of partial disability as a mere physical condition, or must it be both physical and economic? There are a great many workers in dust, perhaps more than we realize, who have definite lung pathology demonstrable clinically and by X-ray, that may be deemed a partial permanent physical impairment, but who have nonetheless a full earning capacity These men do a full day's work, are fully productive and earn full wages when they have jobs Should we say these men must be compensated? If so, for what and how much? We cannot compensate them for loss of earnings, for they have suffered no such loss, nor can we compensate them for inability to get jobs, for they have jobs when work is available Their skill, born of years of experience, has been found in practice to offset in many instances any supposed unemployability due to physical impair-

ment. And unless they make claim for compensation and are physically examined, an employer does not know of the existence of any degree of fibrosis in their lungs, whether partially disabling or not. It is certain in some trades that the workers prefer not to know that they have a mild degree of silicosis, and they assuredly do not wish their employers to learn of their condition through physical examinations. They seem to prefer jobs and the wages that they earn to any compensation allowance, with the certain branding of them as silicotics that would be entailed in any system of compensating for partial disability. They appear to regard that as economically disastrous, and there can be little doubt of the bad psychologic effect of such knowledge.

There is one aspect of partial disability in such cases that is so different from partial disability in accident cases that it should be noted. Partial disability in accident cases, as we see it in innumerable cases, almost invariably is at its worst in the beginning. Usually, as improvement occurs, partial disability follows upon a period of total disability. Partial disability may become permanent when it is found that treatment is of no further benefit, but most often the partial disability becomes less and less until none remains. Not so, however, in cases of partial disability from silicosis or asbestosis In those cases, partial disability, if it arise at all, comes on gradually and insidiously. Physical findings by X-ray are usually the first evidence of the disease. Never is any disability present at the outset. Progress is not toward improvement, but if exposure continue, the disability increases. It may progress to eventual total disability, or the worker may continue working practically to his eventual death If we were to describe the progress of the disability by a curve on the chart, the disability from accidental injury would be shown as a curve downward, while in the case of a dust disease, the curve would be just the opposite—upward.

To the medical man these distinctions may not be very significant, to the administrator and to the insurer they are vital. If a worker is once compensated for partial disability in a dust disease case, it is almost a certainty that he will continue under partial disability until total disability or death occurs And in such a case total disability will not be long in following the partial disability, for once the worker is officially certified as a silicotic his days will be numbered in his trade, and when he can no longer get employment in his trade, he will quickly become an

unfortunate total disability victim Is it to be supposed that his lot in life is thereby bettered through the awarding of compensation for partial disability? His only chance of escape from a complete breakup would be to change his occupation to one in which there is no dust But will he do it? Can he do it, even if he wants to? Bear in mind that these conditions arise only after many years of exposure—fifteen, twenty, twenty-five, or more. In my opinion the worker with that experience behind him will follow his trade to the end, he will not change. And of what use would he be in a new trade? The adage "You cannot teach an old dog new tricks" applies with deadly effect in such cases

Nor can the situation be likened to the condition of permanent partial disability constituting the loss or loss of use of a member or part of a member Such a loss, which is readily ascertainable and measurable, is compensated in accordance with a schedule of benefits set forth in the law, which fairly approximates liquidated damages for the injury sustained. There is little actual relationship between the amount allowed under the schedule in the law and the actual loss of earning capacity The actual loss, however, is complete and the result known There is not the burden of fear hanging over the head of the injured worker that his partial disability will go on to eventual total disability or death On the other hand, in the case of partial disability in a dust disease case, the loss is not at its maximum, it is not accurately measurable, and it is almost certain to be progressive

Efforts have been made to schedulize partial disability in silicosis cases under the laws of some states But because the condition is not static, but is progressive, because there is no practical way of excluding persons so adjudged and compensated from returning to the same or similar employment and thus having their disability increase, and because the payment of a lump sum to a worker so partially disabled is not socially or economically beneficial in many cases, such laws do not, according to the observations of many, work advantageously Under some laws, the return of a worker who has been compensated for partial disability to work in a dusty occupation operates to bar him or his dependents from further compensation in the event of total disability or death following such return to work In some states a worker compensated for partial disability may be permitted to return to his former employment only upon a waiver of further compensation resulting from such disease

Insurance under the law for partial disability would present almost *insuperable difficulties. In the first place*, we have no reliable facts as to the number of workers at any time who have silicosis or asbestosis in any degree, whether disabling in any degree or not. What the exposure is or may be, we have no way of knowing Accordingly, this would raise serious difficulties in the way of fixing rates that would be both reasonable and adequate. The setting of proper rates is at the very basis of effective insurance.

In what has been said, we have not referred to silicosis or asbestosis complicated by infection. When tuberculosis occurs as a complication of a dust disease, there is no question of partial disability. Such a person is at once regarded as totally disabled and should, for the effect not only on himself, but for the safety of his fellow workers, be removed at once from his employment Silicotuberculosis, under the New York law, has not been regarded as a case coming within the limited benefit provisions, but has been compensated in the same manner and to the same extent as tuberculosis, as a complication of any injury due to accident, or to any type of occupational disease other than from harmful dust.

Recalling then the principles referred to at the outset of this paper, it would seem that so far as the New York law is concerned, the obligation for occupational diseases has been made insurable, susceptible of rating and is stated in reasonably definite and certain language. By this, I do not mean to imply that we have no controversial or litigated questions There are always questions as to whether a particular disability is one due to a disease listed in the schedule or whether it may be properly brought within the all-inclusive provision of the law. In the interest of sound insurance, which as I have pointed out is essential to any effective system of compensation, it should always remain so.

Insurance has contributed, and will continue to contribute, of its experience and knowledge of the facts that it has gained in its contacts with the law and its study of the diseases that it has insured. It has contributed, and will continue to contribute as requested, information as to the estimated cost of new measures based upon the extensive statistics derived from the operation of the law in all states. The matter of public policy involved in the enactment of any such laws is the responsibility of the Legislatures, informed by the views of labor and management, and by the responsible suggestions of the administrative authorities. Insurance

may be relied upon in such case to do all in its power to make such laws effective for the accomplishment of the objectives sought thereby.

Discussion

WARREN C TUCKER*

It is either extremely difficult or extremely easy to follow and discuss a paper or lecture by a person having the background, the ability and the wide information, as well as the excellent manner of presentation, as has Mr Sayer It may be that in this instance my task is particularly unimportant because following my discussion you have for consideration a very excellent discussion by Mr Richard C Wagner, who like Mr. Sayer, is a man of wide experience and who will present interesting, carefully prepared, and complete information on this subject

The fact that I am described as being counsel for a mutual company, and Mr Wagner, as everyone knows, represents the stock group interests, makes no difference at all so far as our individual or joint thoughts in connection with such a subject are concerned.

If we are to have a law giving benefits, I hope that insurance companies will have a large part to do with it and will be entitled to issue policies giving protection under such a law, and if there be policies written giving such protection, there will be claims, and in the handling of claims there is no conflict between the stock and mutual groups of the insurance companies

While there have been discussed at this symposium many types of industrial diseases, our compensation law of the state of New York—and I think it is largely to this state that I shall confine my remarks—provides for rather complete coverage for such diseases, with the exception of partial disability resulting from silicosis, and as there is great interest in this particular disease, I shall confine my discussion to it and to the problems of giving compensation benefits to one who may be only partially disabled by reason of it

As Mr Sayer has mentioned in his remarks, the legislature of this state, in providing for compensation for disabled persons by reason of

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occupational diseases, considered at first only specific ones, placing certain restrictions as to the rights of recovery based upon disability from any one of these diseases and the source of these diseases. After certain experience under that law, it was amended in 1935 by providing coverage for "any and all occupational diseases" but restricted this inclusion so that it would not apply to any disability or death due to any disease described in a section of the law known as Article 4-A relating to silicosis. That article gave the sole remedy afforded by the Workmen's Compensation Law to a person suffering from silicosis or any disease described in Article 4-A, and in that Article, Section 66, it was provided "compensation shall not be payable for *partial disability* due to silicosis or other dust disease," and therefore for a worker afflicted by silicosis to recover money benefits under the law of the state of New York, it was necessary that he be totally disabled. Since then the law has been further amended, but the provision requiring total disability before one is entitled to compensation still remains Unquestionably there were in the minds of the legislators reasons for this conclusion.

The original idea, and I think it is still a proper measure for the basis of any compensation law, is to have a statute that compensates a person for an economic loss, and as a practical procedure, we must be able to measure with some degree of accuracy the economic loss which is sustained or which could be claimed under a law giving that remedy

Those of us who are concerned with the approval of claims and with the statute giving certain rights and benefits, expect there will be claims and proper claims to be paid There also will be under any statute attempts to enlarge the clear and unequivocal benefits intended to be conveyed. If a person suffers from an accident and receives a loss of hand, it is a simple matter to estimate and measure the disability. It is a little more difficult to measure the loss sustained when that is loss of use, and that, itself, has proved difficult. There is increasing difficulty in determining the loss of use when the part of the anatomy affected is not readily observable. We sometimes are not satisfied with the appearance as shown by X-rays because the reading of X-rays requires experience and skill not possessed by the ordinary layman, and unfortunately doctors, as well as lawyers, do not always agree in forming a conclusion based upon certain evidence before them. When that evidence is at all obscure, the chances for disagreement multiply

Pneumoconiosis may partake more of the nature of a condition than

the characteristics of what the ordinary person feels is a disease. It may be something like fatigue. A person is somewhat tired, but he is not exhausted. Nature has so endowed a person that the margin of safety between actual disability and a slight impairment of full functions is so great that it seems to me a difficult matter to say this man has a 5 per cent disability; this man has a 10 per cent disability, or this man has a 40 per cent disability. The evidence of this disability is not self-apparent. The nature of the individual, his desire to work, his ambition or his indolence, all play a part in the earning capacity of different persons.

For this reason alone, and as a practical matter, if litigation and contests are to be avoided, the statute giving the disability and the method of ascertaining it should be particularly clear and simple because the disease itself is so obscure and the symptoms vary so definitely in different people that it is most important that those of us who are engaged in the handling of claims and the passing upon the payment of proper claims, as well as the rejecting of improper ones, have a clear and distinct rule of thumb, as it were, to guide us

So far as insurance companies are concerned, there is not and never has been any question but that if the law permits insurance to be written and a premium accepted, it follows as a course that losses must be paid An insurance carrier should be, and is, willing to pay a loss coming within the law, but there should be a specific and definite means of measurement as to what that loss is and when it has occurred What loss is the general public ready to bear, because, whenever an insurance company under a policy of insurance to an employer of the state of New York pays a claim based upon a disability alleged by an employee, the money value of that claim is added to the cost of the goods produced by that employer, and the general public, including the employees engaged in that particular business, as well as all other employees and employers, bear that expense Is the public ready to assume the expense of a law providing for partial disability caused by silicosis?

This is a matter which should be given careful consideration on the part of the general public, and particularly that of the state of New York, because we in New York state feel that laws adopted by this state generally have repercussions and are often followed by other states, and based upon the point of view, the change is sometimes desirable and sometimes undesirable.

Any statute giving partial disability for silicosis should, in my opinion,

be one for real disability. It should not partake of the nature of a pension or for any conditions arising merely from old age or from conditions not traceable, with a reasonable directness, to the employment of the individual seeking benefits

A certain type of employment should not be held responsible for benefits because of conditions developing from other types of employment any more than that particular employment should be held responsible for conditions developing from reasons not connected with any employment in any way.

Probably all of us have a slowing down with the passage of years. Doctors, lawyers, legislators, directors of Workmen's Compensation Boards, all in time and because of the structure of our human body and the passage of years develop certain physical limitations, and if benefits based upon a disability arising out of an employment are to be considered, means should be taken to see, on the one hand, that just disabilities arising by reason of the employment are paid, and at the same time to provide safeguards so that the public will not in the purchase of a product bear an expense not connected with the manufacture of that product.

A reasonably simple rule or procedure should be developed to enable such a law to be fairly and adequately interpreted so that those worthy cases will be given proper consideration, and by the same token, so that the unworthy, frivolous claims, or those which would greatly extend the scope of such statute, will not come within its purview.

During my experience with compensation matters, and particularly during that part of it relating to claims which have been made for silicosis, either based upon the compensation law or the common law, I have never known of a method by which I felt the degree of disability could be accurately and definitely fixed It seems to me that in such cases one party will produce proof of a high degree of disability, and the other party through equally reputable sources will be just as positive that there is little or no disability.

I am somewhat in doubt as to whether a fixed rule can be set up which will deal equitably with all persons, and until a fixed rule can be formulated which will deal equitably with all persons, it would seem that the awarding of benefits to persons not totally disabled should be seriously considered before being finally adopted

The compensation law is a simple, quick remedy for an injured or

disabled employee It would be desirable that any enlargement of our present laws should be capable of interpretation with equal ease and fairness as at present exists.

The injured worker should know when he is entitled to money benefits. Insurance companies should be able to know their liability under the law, and this should be expressed with such clarity that a proper premium can be paid so that not alone will justice be meted out to a disabled person, but the costs of the benefits conferred be capable of ascertainment and by reason of proper premiums be passed on to the general public as a part of the costs of the manufactured article in which work the injured sustains a disability

Discussion

RICHARD C WAGNER*

Mr Sayer, Mr Tucker, and I have been asked to discuss the subject of occupational diseases from the insurance viewpoint This seems to presuppose that this viewpoint is different from that of other persons informed on the subject I question whether that is the case We have all heard Mr Sayer's excellent paper As he has well put it, insurance has no special or particular point of view on the subject of occupational diseases The only point of view it might be said to have is an interest in the adoption of a law that is insurable and in which the rights and obligations are set forth in clear and unambiguous terms I am sure, however, that this is the view of all those interested in a sound law, so that our point of view is not in any sense unique or exclusive

It is true that as insurance carriers we are in a position to observe the operation of occupational disease laws throughout the country to a degree probably greater than any other single group We have to work with and live under these laws on a country-wide basis We can thus know from practical experience what features of the various laws operate the best and are glad to make available to interested persons the benefit of such experience

Mr Sayer has mentioned the desirability of definiteness in this field of

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legislation *I fully subscribe to that thought. Particularly in the earlier* days when comparatively little was known about occupational diseases, it was thought by some that compensation for such diseases could be satisfactorily provided merely by amending the Workmen's Compensation Law by eliminating the requirement that the injury be accidental or by specifically amending the definition of personal injury to include occupational diseases Occasionally, one still finds expression of this view. While at first glance this seemed a simple way of providing this coverage, experience has shown that apparent simplicity, in actual operation, has been transformed to undesirable complexity. Back in 1919, for example, Wisconsin granted such coverage merely by providing that the Act in addition to accidental injuries include all other injuries including occupational diseases growing out of and incidental to the employment In 1936 we find the Supreme Court of that State in the case of Schaefer *v.* Industrial Commission 265 N.W. 390, saying,

> The statute was drawn to cover accidental injuries without any thought of its application to occupational diseases. The right of recovery for injuries sustained by reason of occupational diseases was then inserted into the statute without a revision, so that the terms of the statute applicable only to injuries were required to be interpreted as applied to occupational diseases The court pointed out the defect in the statutory procedure, and did the best it could to make the law workable in the interests of its beneficiaries.

It is apparent that occupational diseases differ in their nature materially from injuries by accident The latter are generally attributable to an event definite as to time and place. In the case of occupational diseases, however, there is generally a considerable period of gradual contraction, extending in the case of some diseases over a period of many years. When does the injury occur, when does the right to compensation arise, when must notice be given to the employer, from what date does the period within which claim must be made begin to run? Specific provisions on these points are necessary Generally, it has been found that the date of disability should govern in this respect.

But even the use of this term is not sufficient. It requires definition. Just what constitutes disability? Is it the time when medical care is first required even though there is no loss of time from work? Certainly from a medical viewpoint, disability would seem to exist at that stage Is it the

time when the occupational disease can first be diagnosed as such? Certainly an injury has been suffered by the employee in such a case although he may be perfectly able to perform his usual duties What of the case where a man may be merely sensitive to some substance in his employment but is suffering from no actual physical incapacity? Can he be considered to be disabled? These are actual cases that were presented to courts for determination in the absence of specific provisions on these points Generally, it has been found that the preferable criterion is the actual physical incapacity because of an occupational disease to perform work This would seem to conform with the general understanding of the term disability and is generally productive of results.

I have mentioned the necessity for definiteness This is of advantage to all parties As a matter of fact, some laws which provide for a broad form of coverage have received more restricted interpretations than those where the diseases have been specifically listed. For example, in Massachusetts the law as originally enacted in 1911 contained no reference to accidental injury but merely to injuries as such Over the years it has been interpreted to cover certain occupational diseases but it was not until 1929, for example, that it was definitely held to cover silicosis More recently in 1940, in Smith's Case, 30 N E 2d 536, it was held that tuberculosis contracted in the course of employment in a hospital where persons suffering from such disease were treated, was not compensable because it was not an injury within the meaning of the law The compensation act of that state has since been amended to cover cases of that type In Arkansas, on the other hand, under the schedule in that state, such a condition would have been compensable in the first place.

Occupational disease cases, moreover, often present difficult medical questions It has been found helpful to have such questions passed upon by a Medical Board. This avoids the necessity of having administrators decide cases on the basis of what sometimes turns out to be sharply conflicting medical evidence For example, here in New York we have a committee of expert consultants on dust diseases Impartial medical opinion in cases of this type is of particular value

Recently, in one or two states, provisions for such Medical Boards have been held unconstitutional, but I believe that those decisions were based on the particular provisions involved in those cases relating to the preparation of a record for review in case of appeal to the courts, and

that properly created there should be no constitutional objection to the existence of such Boards.

Without specific provision, ambiguity may exist unless the law imposes some time limit within which disablement or death must occur If this were not done claims may be made for ailments due to old age and the general hazards of life, rather than the exposure suffered as a result of employment. Some laws provide that the disease must have been contracted within one year from the last injurious exposure Since the date of contraction is often difficult to determine, a law fixing the period as of the last injurious exposure would seem more explicit and, therefore, more desirable.

Another point which warrants specific treatment concerns the exposure to the disease in the last employment As Mr. Sayer has pointed out, most laws provide for liability on the employer who last employed the worker There are sound reasons, however, for limiting this general principle in the case of silicosis and asbestosis by providing that the only employer liable shall be the employer in whose employment the employee was last injuriously exposed for a certain period of time, for example, 60 days Otherwise, liability might be imposed on an employer who had employed the disabled employee for a brief period and manifestly the imposition of a liability for compensation for total disability for an exposure of brief duration would not be equitable

Mention has been made of various features of the law, the specific treatment of which will eliminate to a large extent the field of controversy However, I think we would all agree that it is as important, if not more so, to avoid the contraction of such diseases Prevention should be stressed as well as compensation In this field as well the Saranac Laboratory, in adding to our knowledge about various diseases and particularly the dust diseases, has enabled the adoption of preventive measures It is only by such additions to our wealth of knowledge that the hazards of such diseases can be controlled.

CHAPTER 37

The Management Viewpoint

ANDREW FLETCHER*

The problems of management vary in each industry, and therefore its viewpoints on compensation, as well as on other matters, are very different. I believe that it may be more constructive if my comments are on a rather broader basis, instead of being confined solely to pulmonary and other occupational disease compensation. I am not speaking today as an official of the Industrial Hygiene Foundation, which is a research organization, and therefore cannot take positions on social or economic matters, such as we are at present considering.

Management is being faced with compensation payments for all kinds of various ills, for example, Rhode Island is now paying compensation for sickness in addition to compensation for occupational diseases or accidents, and twelve other states are considering similar legislation. Occupational disease laws are being continually liberalized, such as the New York proposal of partial disability for silicosis. Some unions have, and others are seeking Health and Welfare Funds. It seems to me that in our desire to aid mankind, we are in danger of enacting a lot of laws, creating funds, setting up insurance plans, both private and governmental, without any very well-planned program, or without any very clear idea as to just what the result will be.

It may simplify our immediate problem to consider just why compensation laws were adopted and so to realize how far we have wandered from the original objective of the 1917-1922 period.

In Schneider's second edition on Compensation Law he stated:

Statistics show that approximately 10% of the industrial accidents causing disability are due neither to the fault of the employer nor the

* President, St. Joseph Lead Company, New York, New York, Chairman and Treasurer, Industrial Hygiene Foundation of America, Pittsburgh, Pennsylvania.

that properly created there should be no constitutional objection to the existence of such Boards.

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It may simplify our immediate problem to consider just why compensation laws were adopted, and so to realize how far we have wandered from the original objective of the 1917-1922 period

In Schneider's second edition on Compensation Law, he stated

Statistics show that approximately 40% of the industrial accidents causing disability are due neither to the fault of the employer nor the

* President, St Joseph Lead Company, New York, New York, Chairman and Treasurer, Industrial Hygiene Foundation of America, Pittsburgh, Pennsylvania

employee. Hence, this 40% of such accidents and the additional 30% which are due principally, though not *intentionally, to the fault of the* employee, have not been compensated under our precompensation statutory and common law system, for the reason that compensation or damages under that system depends entirely upon establishing the fact of fault or negligence of the employer as the proximate cause of the personal injury. This means that approximately 70% of the wage loss caused by disability, due to industrial or work accidents, was borne by the workers themselves

What the American workman wants most is security, and he never would have happily accepted the 70 per cent of the wage loss caused by disability. Management rightly accepted the establishment of workmen's compensation laws However, what concerns management is that there are forty-eight States, and forty-seven States have compensation laws with many different provisions. The situation is further complicated within a state—I am told of one company in which they are given different verdicts on the same set of circumstances from compensation boards in neighboring communities within the same state. I am also told that some companies find themselves paying compensation in cases where no time is lost—their words for it are that they are "compensating for the miseries," back pains, etc. Now, what management would like is a uniform compensation law, with only varying compensation rates based on economic conditions in the different states. If such a law should ever prove practical, I would suggest that the maximum allowable concentrations for the safe dust or fume concentration, etc, should not be set in the law but possibly in the administrative codes prepared by the State Departments of Health after adequate information is available. Unfortunately, there are not many Saranac Symposiums, and all occupational hazards are not given the same study that you have given beryllium poisoning and Shaver's disease, during the last four days. In most cases I do not feel that enough scientific data is available for legal enforcement of maximum allowable concentrations proposed for the codes.

Some day industry will have the benefit of a uniform compensation law and codes Even when this happy day arrives, I believe that the following suggestions will be just as practical as they are now:

1. Convince the company or organization that you work for that there is no better way to make money than by lessening accident hazards

The St. Joseph Lead Company has made money by lessening accidents.

In 1923 the cost per $100 of wage and salary roll of our Southeast Missouri Division was $3 51, with 10 cents for safety department expenses, last year it was 58 cents, with 56 cents for safety The indirect cost of accidents is usually figured at three times the direct cost Based on last year's wage and salary roll, the saving per $100 of wage and salary for this division alone was $11 26 (table LXXVIII)

TABLE LXXVIII COST OF ACCIDENTS PER $100 OF WAGE AND SALARY ROLL

	Direct	*Indirect*	*Safety*	*Total*
1923	$3 51	$10 53	$ .10	$14 14
1946	58	1.74	56	2 88
			Saving	$11 26

With a payroll of around 10 millions for this division, the saving in operating costs, including the estimated indirect accident expenses, is over one million dollars per year.

I am also convinced that improved working and living conditions are just as good investments as accident prevention. I am not "hard-boiled," as I am definitely interested in the personal happiness and well being of our employees—but it is usually easier to talk money saving, and not about the happiness that good health and accident prevention bring

2 If your risk is not large enough to be a self-insurer, which I believe is usually desirable, then insure your compensation risk with the company which will make quick and fair settlements. Be liberal, especially in doctor and hospital expenses When an insurance carrier is on the risk, management should still participate in the handling of compensation claims to see that employees are fairly treated

3 Management should at all times take a direct interest in employee relationships, and, as already indicated, one of the most important is workmen's compensation claims Keep away from lawyers, unless you are sure that the claim is unjust—when it is, then employ the best lawyers and fight the claims to the very end, even if the cost of a settlement is less than the cost of fighting the claim.

So much for compensation for accidents, which is the simplest phase of the problem. Now, let us consider occupational disease Certain industries have definite occupational hazards. Industry should and must compensate the injured employee, just as if the injury or sickness was an

accident, whether there is a state law to cover or not. In my opinion, state laws for occupational diseases should have listed coverage and not general coverage, and I do not feel that ordinary diseases, such as pneumonia, should be included, even though in some industries working conditions are necessarily rather severe The costs for protecting the man and his family against occupational hazards should be included as a production cost of the industry However, it must be realized that compensation for occupational disease is much more difficult than for accidents.

Accidents can usually be recognized as such, even by a layman. For example, if an employee is bruised or scratched or has a broken leg, the facts are self-evident. This is not true of occupational diseases which sometimes require very careful examination, including exhaustive tests to make a diagnosis. As an extreme example, we have had a number of cases from our lead smelter at Herculaneum and even from our mining and milling operations in southeast Missouri, where we have no lead poisoning hazard, of employees with appendicitis who have erroneously been diagnosed as having acute lead poisoning. We have had a case filed at our Josephtown zinc smelter, where the only lead in the Plant is in the name St Joseph Lead Company on the stack! It is true that a correct diagnosis can usually be made by thorough examination However, an employee who is told by his doctor that he has "lead colic" and who has some symptoms that seem to bear out this diagnosis, will feel that he has not been treated fairly if he does not receive compensation for time lost—but he is not entitled to any compensation.

The responsibility for industrial accidents can usually be determined without much difficulty, that is, no particular effort is ordinarily required to ascertain if an accident arose out of or in the course of employment. Such is not the case with occupational diseases. If a man, who works in a lead smelter, develops lead poisoning, it is a natural assumption that his lead poisoning arose out of and in the course of his employment, but this is not necessarily true For example, Dr Walmer of the Industrial Hygiene Foundation staff, has told me of a man, who while working over solder pots was closely watched by his employer for signs of lead colic. Although adequate safeguards had been provided, suddenly he showed symptoms of lead poisoning—careful investigation disclosed that the working environment was entirely safe and completely satisfactory. Fi-

nally, the man supplied the clue—he had been spray painting furniture in a closed basement, without ventilation of any kind, and so was inhaling lead at home

Generally, the results of accidents can be determined soon after the accident occurs, and the case disposed of according to the law Results of occupational diseases often show up years after exposure. A man may work in an exposure of free silica and develop silicosis which at the time causes no symptoms He may later, while working for another employer, develop a disabling tuberculosis superimposed on the silicosis. It will be readily seen that although employers may be perfectly willing to accept responsibility for occupational diseases incurred by their employees as a result of their employment with that company, it may be quite difficult for them to avoid responsibility for occupational diseases resulting from exposure elsewhere About the only way employers have of protecting themselves against paying for occupational diseases incurred elsewhere is by (1) a thorough physical entrance examination of each applicant for work, (2) careful inquiry into the previous employment history of each applicant, (3) until second injury laws or waiver provisions have been adopted—rejection of every applicant who has, or may have, an occupational disease incurred elsewhere

If the above practices should be followed bv an appreciable number of employers throughout the country, it would make it difficult for an individual to obtain employment once he had worked any place where there was exposure to conditions that might cause occupational disease This, in turn, would make it difficult for companies whose processes include exposure that might result in occupational diseases to obtain employees—however, it would serve as an incentive to improve working conditions in hazardous plants

In order that employees may not be barred from future employment, states should be very careful about including occupational hazards in their compensation laws until information is available to show that an actual hazard exists When a committee of doctors assumes the responsibility of deciding how disabled a man is, they must be familiar with his work I know of two miners, who from any X-ray diagnosis would be totally disabled, but who today are doing a full day's work In the first place, their silicosis is uncomplicated, and by working quietly and steadily they break just as much rock as the healthy young man who

accident, whether there is a state law to cover or not. In my opinion, state laws for occupational diseases should have listed coverage and not general coverage, and I do not feel that ordinary diseases, such as pneumonia, should be included, even though in some industries working conditions are necessarily rather severe. The costs for protecting the man and his family against occupational hazards should be included as a production cost of the industry However, it must be realized that compensation for occupational disease is much more difficult than for accidents.

Accidents can usually be recognized as such, even by a layman For example, if an employee is bruised or scratched or has a broken leg, the facts are self-evident. This is not true of occupational diseases which sometimes require very careful examination, including exhaustive tests to make a diagnosis As an extreme example, we have had a number of cases from our lead smelter at Herculaneum and even from our mining and milling operations in southeast Missouri, where we have no lead poisoning hazard, of employees with appendicitis who have erroneously been diagnosed as having acute lead poisoning. We have had a case filed at our Josephtown zinc smelter, where the only lead in the Plant is in the name St Joseph Lead Company on the stack! It is true that a correct diagnosis can usually be made by thorough examination However, an employee who is told by his doctor that he has "lead colic" and who has some symptoms that seem to bear out this diagnosis, will feel that he has not been treated fairly if he does not receive compensation for time lost—but he is not entitled to any compensation.

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works so hard for a few minutes that he has to sit down and have a smoke. Before the committee of doctors are able to make any competent statement as to the percentage of disability of any employee, they must be familiar with his work and have some standard as to what is a fair day's work. They certainly can't properly handle a mine case, for example, if they don't take the time to go underground and see just what the working conditions are When the medical committee is thoroughly competent, I feel that their decision should be final and industry should not have the right of appeal.

One often hears it said that the amount of maximum weekly compensation provided for by compensation laws should be increased in line with the increased wage levels and cost of living. There is some merit to this view, as an amount of money that provided a minimum living for a person a few years ago is no longer sufficient for him to "get by." However, it should be recalled that some fifteen years ago, when wages and cost of living were at an abnormally low level, it was thought by many that the amount of compensation paid for disability from accidents or occupational disease was too high. Changes in compensation payment schedules are not easily made, and it is especially difficult to lower the amounts paid If an honest day's work is done, it may be possible to maintain the present high wage and salary rate. If so, then a careful study should be made of the maximum weekly compensation, and on the basis of the cost of living, which varies greatly in the different states It should be remembered that we are all human—and it would be a great mistake to make it more profitable to be sick or injured than fit for a fair day's work We should not forget the adverse effect on the general economy of the 26 weeks' postwar unemployment relief statute

Now in conclusion, I would like to make a few comments about sick leave with pay, paid holidays, sickness and welfare funds, etc I know that everyone is sick now and then, and I think everyone should put aside a reserve for the "rainy day"—however, I do not think that the government, or the state, or the union, or the employer should serve as a nursemaid for the employee, because I feel that the employee and his family should decide how he should spend his well-earned money I am definitely against any policy of paying for time not worked, for paying subsidies for food not planted, for killing little pigs, etc, as the only way to improve the American standard of living is by increasing production,

not by less production Although individual cases can probably be cited to show that such social movements, as sick leave with pay, have done some good and have occasionally kept people from being on charity, the long-term view is certainly most unsatisfactory. Such a policy definitely tends to destroy natural thriftiness in individuals and encourages employees to depend on employers and the government to take care of them under any and all circumstances, all of which must eventually result in national deterioration

If, as is the case with small companies, who do not have sufficient spread to become self-insurers, an employee wishes to join with some of his associates and form a welfare association, or even take out a Hospitalization Plan—such as the Blue Cross—I can see no great objection In the case of a welfare organization or in the payment of claims under an insurance policy, I believe, however, that the employees should handle the claims themselves, because if they do, they will not take advantage of each other, as they often do of an insurance company, especially if an insurance company settles the sickness claims For a five-year period the average payment per employee in our Southeast Missouri Division for sickness coverage under the various Mutual Aid Associations and with an average base payment of $12 33 per week, was $6 00 per year and the cost was $4 88 The best proposal that we have been able to obtain from an insurance carrier was around $11.68 per year per employee, because they felt that they would pay out in claims around $9 50 per year, instead of less than $5 00 per employee as per our Mutual Aid Associations' figures

TABLE LXXIX PER CENT OF SHIFTS NOT WORKED

Group	*Reasons for absence*	*1940*	*1941*	*1942*	*1943*	*1944*	*1945*	*1946*
1	Industrial injury	15	15	16	22	32	43	38
2	Sickness	1 26	1 31	1 04	1 26	2 09	1 98	1 47
3	Personal reasons, including ill-defined and unknown causes, illness or death in family	87	85	1 73	2 30	2 97	3 51	2 60
	TOTAL	2 28	2 31	2 93	3 78	5 38	5 92	4 45

I strongly urge that all companies keep absenteeism figures, and find out just how much time is lost—the above figures for the Southeast Missouri Division are of interest (table LXXIX)

As under the Workmen's Compensation Laws employees are compensated for time lost through industrial injury, we can eliminate this subdivision from consideration in a sickness calculation. I think you will agree that an employee should not be paid for time lost because of personal reasons, so we can also eliminate the third group. Therefore, we are interested in Group 2 which shows the time lost through sickness The average of the above for the seven-year period is slightly less than 1 5 per cent; the time actually lost, on the basis of the employees' own statements to us, is therefore slightly less than five days per year on a six-day week, and less than four days on a five-day week, as workable shifts are between 245 and 255 per year, depending upon the vacation period I know of a company which in the early months of 1946 granted its men 8 days sick leave with pay, while on a five-day week—they actually averaged over 8 days sickness during the next 12 months, instead of their former five-day loss from sickness. It is always a great *temptation* to get something for nothing! What management must do, if we are to maintain our competitive position in the world markets, is to try to guard against indirect wage increases which usually promote inefficiency, such as sick leave with pay, paid holidays, etc.

In my opinion, management should urge states and unions to be very cautious in setting up sickness and welfare funds. Do not let us try to control the life of an individual from the cradle to the grave by various funds, etc —most individuals will take care of themselves, especially if they are forced to Let us pay industrial wages directly and not indirectly by setting up funds However, when funds are set up, then industry *should aid in their proper administration.* I was very pleased to hear that Dr. Sayers will be the Medical Director for the very large fund that has been built by the coal industry Under Dr. Sayers' direction there is at least a fair chance that the fund will be properly handled for the best interests of the contributors—the employees, the employers, and the consumers of coal, who are now paying a higher price per ton.

Provided management, unions, compensation boards, medical committees, and everyone connected with the compensation situation, work together, and with confidence in one another's integrity, I am sure that all of the problems which we are now facing will be readily solved The solution of such problems makes our country greater, and insures a continuation of the American way of life

Discussion

VANDIVER BROWN*

I fear that anything I may have to say regarding the management viewpoint on compensation for pulmonary and other occupational diseases will be somewhat redundant coming as it does after Mr Fletcher's remarks on this subject However, I can at least underscore a few of his thoughts

In the first place, there is not the slightest doubt that the overwhelming weight of opinion in American industry is in favor of compensation for diseases which are *truly* occupational in character Quite properly management measures the problem with the same yardstick it applies to workmen's compensation for industrial accidents As a result it finds that in the long run all the interests involved—the employer, the employee, and the community—are benefited if occupational diseases are compensated in the same manner as traumatic injuries, irrespective of fault on the part of the employer or of contributory negligence on the part of the employee As Mr Fletcher points out, management can justify this view on a purely dollars-and-cents basis without taking into account the imponderable values Although the employer must pay something in all cases, he has a top limit placed on his liability and is spared the hazard of committing the corporate surplus to the tender mercies of a jury with advanced ideas concerning the redistribution of wealth On the other hand, the employee, although he foregoes the gamble of an occasional windfall—generously shared with his lawyer—nevertheless has the assurance of receiving something approximately adequate even though he may have technically "assumed the risk" of employment or been injured by a "fellow servant" or negligently contributed to his injury It follows axiomatically that the community benefits by having fewer incapacitated persons on the charity rolls or on relief

I can think of no better way of illustrating management's view of compensation for industrial accidents and occupational diseases than to tell you what great concern was felt by my own company—Johns-Manville Corporation—when, after having decided to erect a new insulating board

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plant in southwest Mississippi, we learned that this was *the one state* in the Union which had no workmen's compensation law. Of course we went ahead with our plans but we are hoping that early corrective measures will be taken by the state legislature. Mississippi, by the way, has been making rapid progress industrially during the past few years under the guidance of an able and enlightened group of citizens and we feel confident that they soon will be able to remedy the existing situation. It remains our firm conviction that the worst Workmen's Compensation Commission is preferable to the best jury when the issue of compensation for an industrial injury is drawn between a laborer and his corporate employer.

As Mr. Fletcher pointed out, compensation for pulmonary diseases of occupational character presents great difficulties, first, in ascertaining whether the disease derives from employment and, second, in ascertaining the degree of disability. These factors have induced some employers to oppose compensation for pulmonary occupational diseases and have provided sound basis for the argument that, when they are compensated, the law should provide for a well-qualified medical board to determine the existence of the disease and the degree of disability.

While recognizing an obligation for those afflictions which stem from employment, management is firmly opposed to shouldering the burden on behalf of its employees of "all the ills that flesh is heir to" This opposition extends also to tuberculosis as an occupational disease and to general health insurance.

As has been said, management generally favors compensation for *true* occupational diseases, whether pulmonary or other, although it is realized that those of pulmonary character present many special and difficult problems. These problems relate not only to the causal connection between the disease and employment and to the degree of disability that results, but also to the determination of permissible concentrations of dust, fumes, gases, and vapors in those cases where these are responsible for the diseases What is the so-called "threshold limit," on one side of which the concentration can be considered harmless and on the other side dangerous? We realize this is a difficult question to answer but it is one which industry has a right to demand be answered with accuracy and fairness if industry is to be held responsible for eliminating unsafe conditions and for compensating for those diseases that result from operations under unsafe conditions.

Management is not equipped to answer this question but must rely upon the experts in the medical, scientific, and engineering professions State industrial codes are being promulgated right and left which dogmatically—and, I hope, accurately—fix certain mandatory requirements for industries whose processes use, or create, harmful vapors, dusts, etc A tentative draft of one for the state of New Jersey has recently come into my hands, through the courtesy of Mr George Kruger, Deputy Commissioner of Labor Maximum limits are prescribed for a great variety of materials with which I have no familiarity, but it is my earnest hope that these limits have been arrived at on the basis of a better factual and scientific background than exists in the case of asbestos The allowable limit for industries using this material is a "mandatory" requirement of not more than five million particles per cubic foot, *10 microns or less in longest dimension*

So far as I have ever been able to ascertain no one can state with certainty what is the maximum allowable limit for asbestos dust I am certain no study has been made specifically directed toward ascertaining this figure and I question whether there exists sufficient data correlating the disease to the degree of exposure to warrant any determination that will even approximate accuracy It is my guess that the figure was allocated to asbestos either because it had already been prescribed for silicosis or because someone believed, like the poet, that "not failure but low aim is crime" My own efforts to obtain any satisfactory answer from the experts have been greeted with what is sometimes known as a "lawyer-like" comment—that is, an answer that says "Yes and No—or Maybe"

Johns-Manville Corporation and other members of the relatively small asbestos industry have solicited the assistance of experts and have received their wholehearted cooperation, but even the best they could give us has not been enough Experimental work by Dr Gardner here at Saranac demonstrated fairly conclusively that the finer particles would not produce a fibrosis either when inhaled by, or injected into, experimental animals Unlike the situation that exists in silicosis, where the finer particles are the worst offenders, it appears that the large fiberlike particles of asbestos (20 to 50 microns in length and 1 to 3 in thickness) do the damage Unfortunately, Dr Gardner was unable to make a report on his experiments It is our hope that one will be forthcoming before the end of this year based upon his preliminary findings, notes, and conclusions. Meantime, the drafters of industrial codes will presumably con-

tinue to provide us with standards which have no roots in experience but which take their sustenance, like orchids, from the air and, in the case of asbestos, will relate their standards to the innocuous sizes of dust and leave unmentioned those of the character that presumably can have some ill effects.

I mentioned before that most representatives of management are still opposed—and firmly opposed—to general health insurance "Cradle-to-grave" and other paternalistic programs we believe weaken two of the principal supports of our capitalist system, namely, individual incentive—the assurance that for a greater expenditure of effort one will receive a greater reward, and habits of thrift—whereby a person eating beans today may put aside the wherewithal to dine upon sirloins tomorrow or at worst still be able to procure beans for the pot without recourse to charity—either private or governmental. Furthermore, by "saving for a rainy day" (on which one will in all likelihood contract pneumonia) the thrifty soul is also able to afford doses of whatever new wonder drug may be in vogue at the time.

Our strength lies in our productivity Incentive is the spark-plug of production. If we wrap the individual in the cotton-wool of complete security, he will lack incentive and produce nothing. The issue involved in health insurance represents in miniature the world-wide ideological conflict of the present day The opponents of our system have distilled the essence of their philosophy into an alluring epigram. "*From* each according to his ability, *to* each according to his need." At first glance this may seem like the finest flowering of the Christian ethic but this is an illusion The Christian ideal also includes such ancient wisdom as "God helps them that help themselves" and my own Presbyterian dogma includes the doctrine of "original sin." The Marxian dogma, on the other hand, overlooks the Adam that is in all of us Production was unnecessary in the Garden of Eden and Adam produced nothing Most men in a similar situation today would produce nothing. There will be lacking the urgent necessity—the incentive The more talented, industrious, and productive under a perfect socialist state will produce far less than their superior abilities would permit because of their knowledge that they will not enjoy the fruits of their labors The less energetic or intelligent will produce as little as they can get by with because they have been assured that the state will provide for their needs In this economic

climate production will inevitably—in my opinion—fall far below the level of the requirements of more than a fraction of the population At that point, the all-powerful state will be compelled to apply the other means of getting production out of mankind, namely, the lash—forced labor and concentration camps—such as already exist in the Communist states And what of those states that have advanced only part of the way toward the Marxian Utopia? The answer lies in the current situation in Britain That ancient home of the Mother of Parliaments, of Magna Charta, and of the Petition of Rights, after two years of applied Marxism, is now about to engage in the peacetime conscription of labor, a step different only in degree—not in kind—from the barbaric measures long since adopted by the Marxian Fatherland Such steps are inevitable if the paternalistic State is to support its population at even share-the-misery level

You all know the parable of the donkey There are two ways to get him to pull the cart One is to dangle a bunch of carrots a short distance in front of his nose, and the other is to use a black-snake whip or to build a fire under his belly—the last mentioned expedient sometimes resulting in his moving forward just far enough to burn the cart Our own system by and large still adheres to the carrot philosophy and I for one believe that ours is the path of productivity and of power and, as Wendell Willkie said, that "only the productive can be strong and only the strong can be free."

The statistics submitted by Mr Fletcher very clearly exemplify the point I have tried to make They show that if an employer provides compensation for a given number of days of sickness, he will find that the employees will be nonproductive on almost exactly the identical number of days.

A less general objection to health insurance laws, as enacted in Rhode Island and California and as proposed in a number of States, is the disadvantage suffered by an industry in one State which is burdened with these added costs when it attempts to sell its product in competition with that of another industry in a neighboring State which has no such law. We do not believe in laws of this type but if the philosophy of security from "womb to tomb" is to be our doom, let these laws be fitted into a national social security system so that they will be applicable to

everyone equally and at the same time, and let the burden—through taxation—rest on the community as a whole.

Further Discussion

MR. WATERS Thank you, Mr Brown. That was very well done. Mr. Fletcher's paper and Mr. Brown's paper will now be open for discussion I believe we have in the audience Mr. McMahon, the Managing Director of the Industrial Hygiene Foundation of America. Mr. McMahon, would you be kind enough to say a word?

MR. MCMAHON· In the experience of the Industrial Hygiene Foundation, the problems of occupational disease control are shrinking Mr. Nelson referred to the fact that in Wisconsin they had largely eliminated silicosis and that lead poisoning was going in the same direction In varying degrees, I think, that is true throughout the country. The current interest of much of industry is in what you might call positive industrial health.

That is illustrated by a study which we are now undertaking and which will attempt to devise ways and means of protecting men in hot industries from exposure to high temperatures

Occupational disease prevention is usually a matter of improving working conditions. We are currently engaged in working with a large chemical company in the design of a series of new chemical processes with a view to building maximum health protection into the processes themselves The program even includes the instruction of the plant managers in the operation of those plants

Studies are also being made for a number of industrial associations, checking the different plants within the same industry, and reviewing the good and the bad practices The exchange of pertinent information which results helps to improve working conditions on an industry-wide front.

So, the emphasis is on positive industrial health. The Foundation, through the assistance of Dr. C. O. Sappington, has completed a two-year survey of industrial health facilities. Almost three hundred plants were covered in this study, which shows, among other things, that most companies, or most plants, now have some industrial health service.

About thirty-three per cent of them had some industrial hygiene service in varying degrees. The reaction was quite uniform, as Mr. Fletcher brought out, that healthful working conditions are just good business Good working conditions attract a good type of employee and that means a good product

As Charles Kettering has said, "The better the working conditions, the better the attitude of the individual and the better the work." It's pretty clearly demonstrated that this pays off on the economic side, and it is important to bring this out in order to get action

To emphasize the positive approach further, we found in this study that, in more than half of the plants visited, the preplacement physical examination is no longer regarded simply as a measure to determine whether the man has an occupational disease disposition, a rather negative approach, but is used to help in the successful job placement of the individual

We think this adds up to this basic concept there is no longer a question of whether or not industry will sponsor industrial health, but rather, can a company afford not to engage in industrial health activities.

But aside from the tangible economic benefit to management, the immeasurable intangibles are perhaps even greater, for just one thing, health promotes harmony, and harmony is one of those things that we can all use a lot more of these days

CHAPTER 38

Medical Referee's Point of View

DWIGHT O'HARA, M.D.*

In accepting this assignment, I am first of all aware of the limited nature of my own experience and consequently my limited right to express what may or may not be in the minds of others Because there are variations in what the laws require in different parts of the country, as well as variation in the attitudes of different individuals, I cannot hope to develop the viewpoint of the panel physician in a manner that will represent all that has evolved in the minds of those who serve in this capacity It would be a relatively simple matter to state what the viewpoint of the panel physician *should* be, none would quarrel with an idealistic description of the perfect referee—one who sees all, knows all, is infinitely wise and impartial, and whose opinion is always correct. But the panel physician's opinion cannot always be correct It is sometimes a forced opinion concerning the effect of a complex environment upon the even more complex physiology of man And even when it is, or seems to be correct, it may be an opinion that is impossible to substantiate in the minds of those who may not, for understandable reasons, wish to concur

Not long ago I talked with an engineer who found it difficult to understand the principles used by the Almighty in constructing the human body He said if he were to design a machine the responses of which were to depend upon, among other things, a constant pressure of fluid within a system of pipes, that the first thing he would do would be to arrange a pump which delivered the fluid under a fixed rather than an intermittent pressure And when it came to locomotion he said that any engineer would naturally employ wheels instead of trying to balance his machine on these great gangling things called legs This engineer's

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opinion of the human machine was that it was unnecessarily complicated. I think the panel doctor could often share this view, for the complexities of the material with which he has to deal are great indeed The doctor is sometimes forced to form an opinion upon what an engineer would consider insufficient data If the trails of cause and effect are lost in the domain of physiology and pathology, he may find that the available facts really do not authorize him to form a decisive opinion at all, yet he is nevertheless the one upon whom the authority for an opinion seems to have been conferred

Doctors are accustomed to this sort of thing, however, and they have devised ways of meeting it One of the ways to cope with an unknown quantity is to give it a name This masks the fact that little or nothing is known about it and gives everyone a comfortable feeling that somebody understands the issues involved While this may seem fraudulent it is not a complete fraud, for even a tentative diagnosis may become a useful starting point from which further knowledge will be found to clarify the situation On the other hand, a diagnosis may have the opposite effect, becoming the hopeless ashcan into which the whole troublesome matter is dumped and forgotten

The appearance in Massachusetts a few years ago of what has now been called chronic beryllium pneumonitis provided a good illustration of the power inherent in the diagnosis Two medical diagnoses were put forward for this alarming series of cases when they first appeared in the fluorescent lamp industry Neither diagnosis satisfactorily explained the disease or the circumstances under which it originated, but each of them attempted to describe at least one aspect of the condition as it first became known By postmortem examination there had been revealed what appeared to be a chronic inflammatory lung condition which under the microscope resembled *sarcoid disease* This diagnosis however tended to place the disorder in a category which had never been associated with industry, and which psychologically turned its back upon any implication of industrial etiology The other diagnosis was that of *chemical pneumonitis* This, too, was unsatisfactory because the alleged chemical was unknown, but it was used because it retained an industrial interest in the condition until further information might build up a better understanding of what was taking place I think the panel physician would be grateful if it could be more widely appreciated that the diagnosis

must frequently be a working hypothesis rather than a decisive statement of cause and effect.

The diagnosis may be even a description of factual findings and yet fail to elucidate the cause and effect relationships, as the following case illustrates. A man, age 76, was struck by an automobile a year and a half ago. He had been severely hurt, receiving a fractured jaw and a contusion of the chest wall which had been followed by hemopericardium, undoubtedly of traumatic origin Slowly he mended, but at the end of six months there supervened heart muscle failure, and at the time I saw him a few weeks ago he was recovering from his third and most severe attack of cardiac decompensation. He has not been able to work and he naturally believes that his heart attacks are entirely consequent to his injury. Certainly none can say that they are not I do not believe this man will live very long, and the question of whether his death will have been caused by the accident, or by what is not uncommonly a natural cause at the age of seventy-six will be a nice one. The diagnosis may be clear cut—especially if a postmortem examination becomes available—but it may not prove the point at issue. The decision would then become a matter of opinion and compromise, and the doctor may not be able to make any special contribution in spite of the fact that both sides will feel that he should be, or hope that he will be, in a position to support one or the other. I am well aware of the probability that most Boards and Courts would not hesitate to find in favor of the injured party under the circumstances outlined, and I would probably agree with them, but it is possible for the medical evidence to point coldly in the opposite direction

More familiar and less serious examples of the same type of medical indecision are illustrated by the cases of bursitis and hernia that appear in middle-aged employees. Experience has taught us that they are often more expeditiously handled by means of a formula than they are by making an individual appraisal of cause and effect in relation to employment at the time the subject first became aware of the presence of signs or symptoms Middle age carries with it a relative predisposition to bursitis and hernia. As the years advance this predisposition increases, and the amount of exertion in which the individual indulges naturally lessens. Nature intends there to be a balance between these changes in capacity and habit, and such a balance keeps most people out of trouble.

When they do get in trouble the diagnosis may be obvious enough, yet the elucidation of cause and effect may be so manipulated as to invalidate itself if it includes more than a single etiologic factor The more we learn the more difficult it becomes to keep a simplified viewpoint on some of these things

This is also true in the field of clinical medicine, as I recently found when I tried to apply my own experience to the diagnosis of diphtheria in the company of a group of younger doctors who did not know the disease as we used to see it twenty-five years ago We didn't quite agree because we were using somewhat different criteria, but when we called in the expert we found that his greater knowledge did nothing but still further confuse the decision In the end we waited twenty-four hours for a culture to decide whether it was diphtheria—and that is a very poor way to treat that disease Now this struck me as a surprising turn of events, that one of the diseases concerning which we have indisputably accurate knowledge should have become more difficult to recognize and thereby less efficiently treated The reason for this paradox is that in applying our knowledge we have all but eradicated our experience, and have thus forced the subject from the center of our thought and action to the periphery where, even in the minds of the experts, its practical aspects may become sparse and poorly delineated

The same phenomenon appears in some of industry's historic interests, such as lead and mercury poisoning. If we could wait until the advanced symptomatology unfolds itself in these disorders we would be on familiar ground and we could afford to be unequivocal and decisive, but that is too late We must work in the peripheral areas of our knowledge, for that is where opinions differ, and unless there are differences of opinion the panel physician *is not likely to be called upon Also it is in this* peripheral area that all industrial medicine and hygiene must operate, for it is only here that prevention can be practiced and that the health of the worker can be effectually protected

Even when the basic disorder and its etiology are agreed upon by all sides, there may still be controversy concerning such things as the percentage of disability to be allowed Here again when the doctor is called upon he misses the engineer's ability to measure and accurately to determine percentages of efficiency The human, personal, and psychologic factors of the individual intrude themselves into what we would like to

consider a scientific field—and what might be a scientific field if the doctors were to be left alone in it. It would be an ivory tower, however, and the medical profession in an ivory tower would soon lose its usefulness to industry and to society. These are not the only times when doctors find that their opinions are complicated by psychologic and sociologic considerations Sickness, when it can be verified, is an inviolable excuse for all sorts of inconveniences to the individual; for examinations for which a student is unprepared, for embarrassing appearances in court, or for absence from duty or employment The doctor is therefore accustomed to having his opinion built into situations in which the health of the individual may not be the only issue at stake. Indeed, if it were the only issue at stake the doctor might well take the attitude that loss of health is never completely compensable, he would then ignore all implications of liability and would concentrate on the regimen which would best serve restoration of health This is his usual outlook in the practice of medicine, but when he is employed as a panel physician he cannot retain this objective, he must concentrate upon an accurate presentation of the facts, and then stop This is not the physician's usual habit of thought and action, if it were he would frequently leave his patient on the end of a limb He generally goes beyond the proven facts to build a working hypothesis, and proceeds with whatever guidance such hypotheses provide until there is obviously nothing more to do for the patient For the panel physician to proceed in this way in an industrial controversy would be to violate the legal rules and might jeopardize the interests of others. In this regard the panel physician is better called a medical witness The great traditions of the medical and legal professions here run side by side, as the tracks of competing railroads approaching a common destination

Three hundred years ago Sir Thomas Browne said it was "as dangerous to be sentenced by a Physician as by a Judge" This is no longer true, even in its original sense. The doctor doesn't sentence his patients any more In the settlement of industrial controversies I do not believe the doctor should be expected to do any sentencing; he should be merely a witness His testimony should be reviewed or revised if need be by a court or board or whatever the individual law indicates, and it is this court or board that should assume responsibility for the decision It should be the judge, while the doctor concentrates on being a comprehensive and impartial witness.

My idea of the viewpoint of the panel physician may be summarized by indicating that

1 He is primarily concerned with cause and effect relationships, especially as they may imply industrial or other liability for initiating causes
2 He is but secondarily concerned with what would normally be his primary interest, that is, the restoration of health to the individual subject.
3 He is in essence a medical witness, and should not presume or be expected to make the decisions He should merely state his opinion.
4 His opinion must sometimes of necessity be a tenuous one, for an honest statement of what is known about etiology will frequently reveal that much is still unknown Moreover, dual causes for some conditions are already well established

I have tried to present the reasons that the panel physician's contribution may sometimes be a disappointment to those with whom he works. There is a widespread belief among the people at large that the doctors know more than they actually do, and that they can do more than they actually can The controversies which arise in a well-explored area of medical knowledge do not often call for difficult medical analysis Those which arise at the periphery of our knowledge, however, may present serious problems of a fundamental nature A solution for these problems may be needed before a direct light can be thrown upon the prevention or the equities of compensation and disability for some industrial diseases In the meantime as we grope about in these poorly illuminated fields none can be certain of providing the perfect answers It is as true today as it was when it was written, I believe in the *Anatomy of Melancholy*, that "there are not only diseases that are incurable in Physic, there are cases insoluble in Law and vices incorrigible in Divinity"

Discussion

H A BRODKIN, M D *

One of the most valuable contributions of the Sixth Saranac Symposium has been the official recognition that employees working with beryllium

* Chief Medical Director, New Jersey Department of Labor, Newark, New Jersey

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and its compounds are exposed to a new industrial hazard which may result in a new industrial disease. This disease may appear in the acute form, acute pneumonitis of beryllium workers, and in the chronic or delayed form, pulmonary granulomatosis of beryllium workers. Inasmuch as the acute form ends in complete resolution or death, it presents no particular problem as far as estimation of the amount of disability in the compensation bureau is concerned. The chronic form of the disease, however, does produce permanent pulmonary damage which so far in the large majority of cases appears to be progressive.

Dean O'Hara, in his paper, has dealt with the problems of the medical referee in deciding on the industrial etiology and the amount of disability. He has pointed out the pitfalls, complications, and the intangibles that hinder a medical referee in arriving at a mathematical and equitable decision. Judgment greater than that of Solomon's is needed to satisfy all parties concerned The compensation aspects of this new industrial disease are a perfect example of the difficulties described by Dean O'Hara. Here we have a disease, which affects one worker among scores of others, who may have been exposed for years on the one job without ill effects, and who may suddenly develop the disease or develop it several years after he had last been exposed to it. Furthermore, the strongest evidence of the disease, the roentgenogram, may be so equivocal as to make it difficult to differentiate between pulmonary granulomatosis, *tuberculosis, sarcoidosis, lymphatic carcinomatosis, fungus disease,* or some other form of pneumoconiosis So much for the difficulty in arriving at the industrial etiology.

In attempting to estimate the amount of disability in a case of industrial pulmonary disease, we are beset with two difficulties First, it is complicated by the fact that the amount of disability is estimated by the loss of earning power The difficulty is apparent when we see a man with extensive enough disease in his lungs, as seen in the roentgenogram, to be considered totally disabled, performing a normal day's work because of his economic drive and necessities, and then compare him to a man with half as much involvement, as seen in his roentgenogram, who claims he is disabled and must change his job. Thus far, with our X-rays, blood studies, chest measurement, and vital capacity estimations, we are unable to accurately measure the amount of disability or loss of working capacity

in cases of industrial pulmonary disease The estimation of maximum breathing capacity may prove an advance toward this goal but much further work must be done to produce a more accurate yardstick.

In New Jersey, silicosis and asbestosis were added to the existing eleven occupational compensable diseases in 1945 The statute on silicosis provides that compensation shall only be payable to the employee when total disability results from this disease. No provision is made for the payment of any compensation to an employee who is partially disabled The statute specifically takes away an employee's common law right to sue for partial disability. An employer can discharge any employee who has silicosis or asbestosis and who is not totally disabled, without paying any compensation and yet no other employer would hire such a worker who is partially disabled. There are many other features of this statute that are unfair and deplorable and suffice it to say, that I personally am not aware of a single employee receiving compensation under this statute, although New Jersey has many industries where silica and asbestos are a hazard.

Obviously, the ideal and desirable industrial disease law would be an all-inclusive one, but one in which the industrial relationship and amount of disability would be decided by a competent state medical board In this way, industry would be protected from all false claims The pulmonary disease of beryllium workers should be included in our compensation law, otherwise our beryllium industries are forced to pay not only compensation premiums but also liability insurance

Further Discussion

DR. McGEE It occurs to me I should make an explanatory comment on an impression I did not mean to give this morning Dr Mayer, I believe, in discussion came to the defense of medical witnesses and used the term "perjury." I did not wish to imply that in my experience that was the problem. The opposite is true The untenable decisions have come from a lack of information on the part of men who were well-meaning and sincere in their testimony. That has gotten us into difficulty.

The character of people who are getting into the picture in compensation decisions is of high caliber—it's improving rapidly—and some of

our difficulties are going to disappear. We hope their advice will be used more and more in evaluating the testimony.

There have been two or three speakers who hammered a pet project of mine—that of education on the functions the physician performs in this complicated society. Our profession started off with the basic aim of relieving the distressed and ill and of contributing to longevity. In addition, doctors now must certify to a man's birth and his death and to much of what transpires in between Industry requires statements from physicians—in the late war we had ration certificates shoved at us from time to time The profession knows well the other "slants" that are required for the proper fulfilling of its function Education can be aided if Mr. Bowditch and Mr Waters will see that the stenographic record of this symposium appears in a volume and reaches the deans of medical schools, professors of medicine and others concerned, so that they have a better appreciation of the opportunity to be of real service in this matter.

I was reminded by Dr. O'Hara's statement, when he referred to the physician's tendency to give a name to a problem he may not understand too well, of this story The physician was on the witness stand in a trial by a jury The physician under cross examination was protecting himself by using "two-bit" words with Latin endings Obviously no one of the jurists nor any other lay person in the court understood The cross-examining attorney interrupted with a sly wink to the jury and said, "Yes, doctor, and if you do, you'll have to clean it up"

MR WATERS Thank you, doctor. Dr Herman, in your experience as Chairman of the Maryland Medical Board, would you tell us something about your work that would be of interest on this subject?

DR. HERMAN: As I understand it, the situation in Maryland regarding the administration of the compensation law is somewhat different from other states in that the Board has been appointed to consist entirely of medical men, one of whom by statute should be a radiologist. I should state parenthetically, that Mr Waters should tell you of the Act, because he's the "father" and "grandfather" of it

This Board is set up within the framework of the Industrial Accident Commission of the State. The Commission, of course, is a much older body and is charged with the hearing of compensation claims for accidents alone.

The Medical Board, which was organized in 1939, hears the claims for compensation for occupational disease according to a scheduled act We're not confronted with the problem of the panel physician or medical referee, inasmuch as we fulfill that function

We're strongly opposed, as has been mentioned, to ex parte testimony We have been trained in, or have had enough knowledge of industrial hygiene and of the occupational hazards involved to have a point of view on the subjects, if that point of view isn't adequate, we're empowered to obtain further information.

Our problems are tremendously different from the problems that have been discussed here in that Maryland is but slightly industrialized, as compared with the states whose problems have been specifically discussed Outside of Baltimore, in which there is a diversification of industry, there are only two other cities from which claims for compensation for occupational disease arise—occasionally from a third So our problem is really quite different

However, within that scope, I think that many of the pitfalls that have apparently assailed the rest of the country have been avoided by the way that claims are referred to a technically trained body

The Legislature is not unaware of the changing picture. Maryland being in every sense a median state, its recognition is much different from, let us say, New York in that respect In the last Legislature, five new items were added, diseases resulting from contact or exposure to antigenic substances, to selenium, tellurium, fluorine, and brucellosis, and there is a constant pressure to extend the list

As to the question of general coverage versus scheduled coverage, I certainly don't want to go into that again

MR WATERS. Thank you, doctor Does anyone else have any thoughts to contribute on this particular subject?

DR SAPPINGTON I should just like to say a few words on industrial medical education, a subject brought up by several of the speakers Perhaps it might be of interest to you to know what is and has been going on quite recently in official bodies

The American Association of Industrial Physicians and Surgeons, about three years ago, appointed a joint committee to study certification of industrial physicians This committee made very little progress, primarily because of the fact that the certifying bodies pointed out there

were great deficiencies in both undergraduate and postgraduate education in industrial medicine, and that these deficiencies would have to be remedied, to which all agreed.

Within recent months, and this is where progress has really been made, several representatives of the association have gotten together and have prepared criteria for fellowships and residencies in industrial medicine, truly a significant step. These criteria will undoubtedly be accepted by the Council on Medical Education. They are going through that process now, which leads us to believe that eventually there will be official recognition and sponsorship by organized medicine of industrial medical education in this country, something which many of us have wanted for a long time.

MR WATERS. Thank you, doctor. Anyone else? This morning Dr. George Wright said he wanted to speak this afternoon.

DR. WRIGHT: It's very generous of you to let me have just a moment. Some of the things I thought of saying have been ably covered by others, so I don't want to take your time further with them, but I do want to explain for just a moment the way in which we got into this present study of partial disability, because it portrays the very happy circumstances that have occurred in recent times apropos this program of compensation.

The study is being supported—and that is the thing I want to make very clear—by a joint effort of labor and management, the federal government, the New York State Workmen's Compensation Board, and through them, the Legislature of New York State. We are obtaining some funds from Miss Donlon's office. We are obtaining some funds from the federal government The men are giving us their time, the laboring men, and accepting the inconvenience of coming up here to be studied, and management is paying the wages of the men to be studied

I think this arrangement is one that should delight the hearts of all of us who have the future of this problem in mind because it is a real constructive effort on the part of everyone involved to get to the answer of the problem we are studying in a specific way. I just didn't want the day to go by without that information being in the record.

The only other thing I would like to say has some bearing on the problem as a whole—that is, I fear that some who perhaps should know better do not realize or have forgotten that medicine is not wholly a

science It is in a large measure an art. It is a science only insofar as we can apply measurable things to it. When one can begin to measure in specific quantities anything you are studying, then you can begin to speak of the study as scientific, and in medicine that is still, unfortunately, not very well developed

To me that explains in a large way the apparent controversial points that have been raised here today. I am afraid that in some aspects legislation has outstripped the scientific aspects of medicine, and that, I think, is a thing to be deplored. It's perfectly obvious to you that in New York State at least—I think largely through Miss Donlon's efforts—they are trying to remedy that particular circumstance They do not wish to enact new legislation without first obtaining some information concerning the measurable features of the things they are going to legislate about

MR WATERS: Thank you, Dr. Wright Dr Mayer, would you say just a word in comment?

DR MAYER I'm sorry I gave Dr. McGee the impression that I was particularly referring to his remarks. Actually, the question of perjury has come up so regularly in our work that only recently I tried to define whether there really was much perjury on the part of the doctors On going through the records, we rarely could say we were sure this doctor definitely knew otherwise There's no question about the need of the education of the doctor, and therefore undoubtedly the testimony at present is given through ignorance.

One term that constantly comes up that has been very annoying to the physician in industrial medicine is "compensation doctor." Better physicians often shy off from testifying because of the stigma many attach to it

We three on the consulting board had much to do with getting Dr. Wright into his "troubles" We can't say necessarily that the functional disability tests are going to be our answer. But we quite often meet patients not totally disabled, where, as Dean O'Hara said, our opinion is tenuous and these disability functional tests we're hoping will help us

Up to now we've had a fair number of these tests done for us at Presbyterian Hospital under the direction of Dr Baldwin and Dr Richards, in addition to the studies of Dr. Wright At times they have

given us courage to "stick our necks out" and give positive opinions which otherwise would have been lacking. Someone asked how our Board functions. Controversial cases are seen by our group of three that meets every few weeks in New York City. We have gone over the cases individually and then the reports are scrutinized by the other two as they are presented at the conferences We encounter probably every dust inhalation disease there is.

We are particularly fortunate as "impartial" examiners to be allowed to so assert when we don't know the answers. We are privileged in doubtful cases of disability to have functional studies carried out in the hospital This is in addition to having complete occupational history, physical examination, all laboratory studies including electrocardiograms, fluoroscopic studies, X-rays, blood chemistry, etc. We give our opinion on all such data. Some workers with minimal X-ray changes impress us as very dyspneic, particularly foundry workers. These men at autopsy showed much interstitial fibrosis with emphysema, and their disability studies in life showed marked functional impairment Some with little evident silicosis have much emphysema and are quite disabled, some with good reserve have much evident silicosis and little emphysema

CHAPTER 39

Synthesis of Viewpoints

THEODORE C. WATERS*

As stated in my opening remarks, I feel certain that all of us are not agreed upon many of the issues that have been discussed at this meeting, but I am sure that this symposium has made a real contribution to the current thought upon compensation for occupational diseases

Dr. McGee, in presenting the viewpoint of the medical practitioner, develops certain thoughts that I believe should be emphasized. He expressed the opinion that all occupational diseases should be made compensable under the compensation statutes That seems to be the general opinion of the members of the medical profession While that goal is admittedly desirable, I feel that he properly pointed out the potential hazards of general coverage laws To me, the most significant part of his remarks related to the wrong that might be done to a claimant and his fellow workers from unjustified awards in compensation cases Attendant neurosis and the general belief that a claimant can get something for nothing may react detrimentally to those employees who suffer real injuries. His remarks relative to the need for emphasis upon industrial medicine in the curricula of our medical schools were most timely Unfortunately, too little emphasis has been placed upon this important phase of study and I believe it would be desirable for our medical schools to take cognizance of their responsibility in this connection

Dr. Sander in his inimitable way presented to us the unfortunate result that may occur in the administration of compensation laws when employees who have limited evidence of occupational disease are denied employment in given industries In the course of the administration of compensation laws, it is to be hoped that the human scrap-heap may be avoided and that those able to do a given job will not be excluded from

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employment simply because they have a nondisabling occupational disease.

Miss Donlon, the chairman of the Workmen's Compensation Board of New York, has presented to this meeting real food for thought. I would be less than frank if I did not state my disagreement with some of her recommendations and purposes. She and her office have given thorough consideration to the administration of the law of this state and to her may be attributed the liberalizing amendments that were enacted at the last session of the State Legislature. Those of us in other states are going to view critically New York's experience in the administration of this new law. Because the pattern set by this state may well be followed in the industrial states of the Union, I hope that all of you have and will carefully consider her remarks and that you will pay particular attention to the increased scope of the Second Injury Fund Law of the state of New York to which she has referred.

Mr Nelson speaks from the experience in the administration of the Wisconsin law that has served as a model for other states to follow. His remarks about the subject of physical examinations are most timely. The proper use of physical examinations for placement of employees in industry will be highly beneficial not only to the industry concerned but also to employees about to be subjected to potential industrial hazards. In this connection, I feel that Wisconsin's experience in the administration of its law applicable to compensation for silicosis should be a lesson to the other states that are perplexed with this problem.

Mr. Sayer, presenting the insurance viewpoint, developed several thoughts that I believe are of interest to all of us. With his usual effectiveness he stated that the function of insurance was to make certain compensation to injured employees for such injuries. He advocated that proposed laws should be definite and certain in their language and statement of purpose, avoiding controversial issues that might be the subject of litigation between claimants and employers. His remarks with respect to the subject of potential compensation for partial disability from dust diseases were most timely and should be considered carefully by those who believe that such compensation would be a boon to employees. Insurance has a real responsibility and function in this field, and any proposed law should be properly insurable.

Mr. Tucker, speaking from his experience in the handling of compen-

sation matters, has added a timely note about the basic purpose of compensation statutes for economic laws and develops responsibility of carriers to insure the payment of compensation for that loss.

Mr Wagner has appropriately presented the need for definiteness in compensation legislature, and has developed the insurance carrier's viewpoint with respect to the need for proper solution of medical consideration involved in controversial cases

Mr Fletcher presented the viewpoint of management, and pointed out the hazards of establishing insurance plans and help funds without a well-considered basis for such programs. He stressed the financial saving to management by lessening the hazards of accidents, and emphasized the need for interest by the employer in the health and welfare of employees His approach was thoroughly practical and I commend to your consideration his comment about sickness and welfare funds, paid holidays and other benefits to employees that might lull them into a feeling that management would assume all responsibility for their ills

Mr. Brown's story emphasized the need for greater production in order to promote the general economic welfare of our people I think his comment upon state insurance laws is particularly pertinent and his remarks raised in my mind the burden that may be imposed upon industry in one given state, where it may be competing with that of another state where such laws are not effective I was indeed glad that he referred to the matter of formulation of codes. This is most timely and should be carefully considered by those industries that may be affected by such codes

Dr. O'Hara told of the problems that face the panel physician in passing upon disputed clients and their effort to relate the fact of injury to plant conditions causing same He stressed the function of the examiner as a medical witness and that the physician's findings should be an expression of medical opinion on disputed medical issues

Dr Brodkin, speaking from his experience with the administration of the New Jersey Workmen's Compensation Law, pointed out some of the problems applicable to compensation for dust diseases From his remarks it is apparent that the occupational disease provisions of compensation statutes present peculiar problems to the administrators, indicating the need for competent medical examiners and advisers in order for the bureau to determine controverted medical questions

I repeat my regret that representatives of labor are not here to express

their viewpoint in the subject matter of our discussions because it would be helpful for those of us concerned with the administration of compensation laws to know what the representatives of labor want and in round-table discussions with them find some solution of our common problem.

CONCLUSION

May I remind you that the subjects that have been discussed at this symposium are essentially controversial. Many of the compensation laws are exceedingly complex, verbose, and capable of varying constructions.

The burden that we have placed upon our administrators of these laws is not an easy one. The administration of even a law that is practically perfect in form may still not prove to be successful. I would like to stress the importance of administration and suggest that administrators should avoid an attitude of awarding damages for alleged injuries, but should seek to grant compensation to those cases where the employees have suffered actual wage losses as a result of their injuries This system of law is social in its nature and should be administered in a manner that would give to the claimants the benefit of reasonable doubt However, the administrators should avoid the concept that these laws are designed to compensate for all human ills, with resulting imposition upon employers of costs not proposed to be imposed under the basic theory of the law

I would like to say one word with respect to the compensation statutes in the various states To me it seems unfortunate that there has not been a movement on the part of employer and employee organizations, insurance carriers, or those interested in the successful administration of compensation laws to bring about some uniformity in this legislation Every state has a law unto itself, with varying provisions as to the scope of coverage, benefits payable, and methods of administration. If some type of uniformity could be achieved in the basic framework of the laws, I believe that their administration would be more successful

There is one further subject that I would like to touch upon One of the principal purposes sought to be accomplished by the Workmen's Compensation Laws has been to reduce the total injuries sustained by the employees in the course of employment. In practically every one of the

laws you will find provision made for supervision, regulation, and control of industrial operations, with the assignment of factory inspectors to enforce compliance with the law In spite of the tremendous advance that has been made in accident prevention, the toll of industrial injuries continues to be appalling Employees and the public generally are justly demanding that this toll be reduced This can be accomplished if management and employees adopt and administer an intelligent program of industrial hygiene. Much has been accomplished in this field Much remains to be accomplished By the cooperation of employees, employers, insurance carriers, and state administrative agencies, the goal of industrial hygiene should be attained and the cost of compensation under these laws materially reduced

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September 29 to October 3, 1947

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